Original Communications

THE MORPHOLOGY OF THE GENITAL EPITHELIA, WITH SPECIAL REFERENCE TO DIFFERENTIATION ANOMALIES*

Emil Novak, M.D., Baltimore, Md.

(From the Gynecological Department of Johns Hopkins Medical School)

WHILE the genital epithelium presents marked histologic differences in different segments of the genital canal, there is a close kinship between these various epithelia, because of their common derivation from the same mother tissue, the coelomic epithelium. This is in accord with a general law in embryology, as expressed by Fischel,[1] that tissues derived from the same mother tissue are not only closely related, but that they possess a considerable degree of interchangeability. The purpose of this paper is to stress the fact that manifestations of such intermutability of the genital epithelia are not uncommon, and that this must have an influence upon our interpretation of certain pathologic pictures.

The mother tissue of all the genital epithelia is the coelomic epithelium covering the wolffian body. Shortly after the appearance of the primitive sex gland area, when the embryo is in about a 10 mm. stage, there appears just craniad to the sex gland region the infolding of the coelomic epithelium which is to become the muellerian duct. The caudal growth of this duct, and its later partial fusion with the duct of the opposite side to form the genital tract, need not here be redescribed. The point which may be reemphasized, however, is that the various epithelia of the genital canal represent merely different degrees of differentiation of the original coelomic epithelium.

To put it another way, the coelomic epithelium is, so far as the genital canal is concerned, a "totipotent" one, being capable of forming ovarian, tubal, uterine, cervical or vaginal mucosa. The ovarian epithelium, representing a coelomic epithelium which has, so to speak, used up only a small proportion of its differentiating potency, is likewise capable of much further differentiation, into tubal or uterine epithelium, for example. And so, in diminishing ratio, with the more highly differentiated epithelia, so that, for example, the stratified squamous epithelium of the vagina is a far more fixed one than that seen elsewhere in the genital canal.

The remarkable purposeful adaptation of structure to function is nowhere better illustrated than in this segmental differentiation of the genital epithelium. For example, in a structure like the tube, designed chiefly for transport of the egg from the ovary to the uterus, ciliation is more highly developed than elsewhere in the tract, and the tubal muscle

Fig. 1.—Section of fimbria ovarica showing an epithelium consisting entirely of ciliated columnar cells, with no secretory cells whatever, although a few of the latter are at times seen.

is present to assist in propulsion. The mucosa of the fimbria ovarica is covered by cells practically all of which are ciliated, to create the ciliary stream which directs the egg from the ovary into the open mouth of the tube. (Fig. 1.) The endometrium, among other teleologic attributes, possesses an amazing regenerative faculty, so that it can restore itself *ad integrum* almost within a period of hours, and with no scar tissue to tell the tale. Such a property is unique among the tissues of the body. A similar purposefulness may be discerned in the structure of the cervix and of the vagina.

From what was said above, it might be inferred that the direction of the differentiation wave, so to speak, is always from above downward, but this is not necessarily the case. For example, areas of retarded development may often be seen, so that the mucosa at any level may show a degree of differentiation characteristic of a much higher level in the canal, where the differentiating process is not so far advanced. These facts are here stated rather arbitrarily, but I believe they are in con-

formity with facts, aside from possible differences of opinion as to what constitutes a high and what a low degree of differentiation.

We are of course just as ignorant of the forces behind the differentiating processes in the genital tract as we are of similar changes in other systems of the body. Nor can we speak with any knowledge of the cause of localized anomalies of differentiation, such as I expect to discuss in this paper. Whatever the underlying cause may be, it is not easy to understand why these anomalies affect only small areas rather than whole segments which are presumably under the influence of the same cause. The view held by many, and championed especially by Robert Meyer,[2] is that such localized abnormalities of differentiation involve only certain indifferent cells, which have remained slumbering among their more active fellows until some stimulus awakens them to differenti-
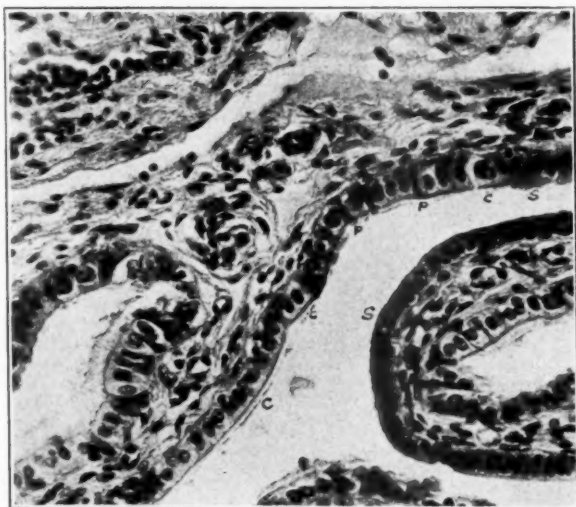

Fig. 2.—Normal postmenstrual tubal epithelium, showing (C) ciliated (nonsecretory), (S) nonciliated (secretory) cells, and (P) peg-cells.

ating activity. Under this impulse they begin to differentiate, reaching stages either behind or ahead of their fellows. There are thus produced areas of over-differentiation or "prosoplasia," on the one hand, or under-differentiation or hypoplasia, on the other. The term hypoplasia in this connection, as used by Meyer, is not a happy one, as it is more commonly applied to gross changes. Perhaps retroplasia would be a better designation.

The theory thus enunciated, based though it is on the assumption of an indifferent type of cell not detectable histologically, appears to be a rational one, and will at least furnish a working basis in the explanation of the histologic abnormalities which furnish the incentive for this paper. Some of these are frequent, some rare, but, in the examination of a large material, I have been struck with the relative frequency of the group as a whole. I shall discuss only the more important among them.

SOME DIFFERENTIATION ANOMALIES OF TUBAL EPITHELIUM

The tubal epithelium may be considered first of all, because it is a sort of intermediate type between that of the uterus and that of the ovary, and because it, more than any other, presents certain characteristics which appear rather generic of muellerian mucosa. Its normal histology need not be reviewed, except to recall the fact that it is made up of two chief types of cells, one ciliated and nonsecretory, the other nonciliated and secretory. (Fig. 2.) The distribution of these cells varies in different parts of the tube, but they are fairly evenly divided. The striking changes seen in these cells at different phases of the menstrual cycle constitute the tubal analogue of the much more conspicuous menstrual cycle of the endometrium. They have been described in a previous paper by the present author, in collaboration with Everett.[3]
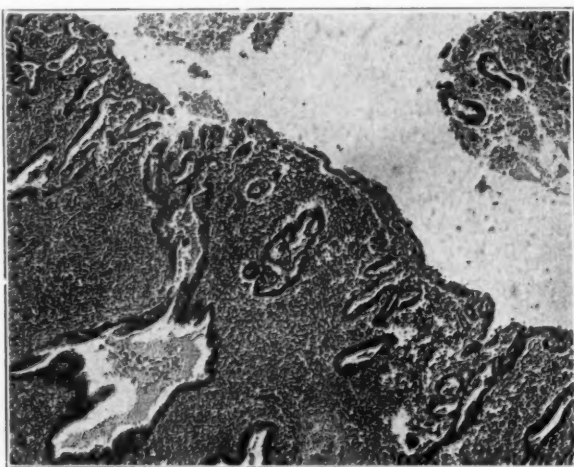

Fig. 3.—Section of tubal ampulla, showing marked inflammatory change, with an endometrium-like picture quite different from that ordinarily seen. The epithelium is of the uterine type, there is a hemorrhagic exudate in the lumen, and the patient has just menstruated. The free bit of tissue in the lumen, apparently thrown off from the tubal surface, looks like desquamated endometrium.

A third type of cell, the so-called peg-cell *(stiftchenzelle)* adds to the distinctiveness of the tubal epithelium (Fig. 2), so that one is accustomed to speak of an epithelium showing these three varieties of cell, and especially the first two in characteristic distribution, as a tubal type of epithelium.

The most interesting anomaly of differentiation encountered in the tube is represented by the finding of definite endometrium in larger or smaller patches, sometimes even encircling small segments of the tube, and often separated from the endometrium of the uterus by broad stretches of normal tube. This abnormality is not common, but I have encountered it a number of times, and a considerable number of such observations are to be found in the literature. Aside from the cases in which perfectly frank endometrium is found, with characteristic epi-

thelium, glands and stroma, there are many instances encountered in which the mucosa represents only an approach to the endometrial type, with gland-like arrangement of the folds and an imperfect stroma.

Of the specimens studied which show this endometrium-like mucosa in the tubes in varying degrees of frankness, two are especially pertinent to the present discussion.

CASE 1.—This patient, a colored woman of twenty-four, had suffered for many months with lower abdominal discomfort and severe dysmenorrhea, and examination revealed bilateral chronic salpingitis, for which double salpingectomy was done on December 19, 1931, just after a menstrual period. The gross examination of the tubes

Fig. 4.—Section of tubal ampulla, showing, above, the endometrial lining, with invasion of the muscular wall (adenomyoma of tube). The latter shows uterine epithelium, glands, and stroma. Below and to left is another smaller invagination, without stroma and with tubal epithelium. A number of similar invaginations are seen in other parts of the section, one being shown under higher power in Fig. 5.

presented no unusual features, both being thick-walled, filled with a brownish exudate, and the fimbriated ends being closed.

Microscopic examination showed a marked degree of chronic inflammation, involving the muscularis as well as the mucosa. The especial point of interest in the latter was the striking resemblance to endometrium seen in many of the sections. (Fig. 3.) The gland-like pattern was quite different from that seen in many cases of follicular salpingitis, and the epithelium lining the glands was of the uterine rather than the tubal type. The stroma showed so much inflammatory infiltration that one could not be sure of a resemblance to endometrial stroma. In some areas there was a picture not unlike that seen in the uterine mucosa in the menstruating stage, and bits of mucosa, apparently thus cast off, could not be distinguished from endometrium. The presence of many red corpuscles in the lumen, with of course also leucocytes, further suggested that a tubal menstruation had actually occurred. This, in view of the histologic appearance of the tubal mucosa, appeared more likely than that the blood and endometrial particles had regurgitated from the uterine cavity.

CASE 2.—The patient, a colored woman of thirty-two, was operated upon January 16, 1932, just at the close of a menstrual period. The operation consisted of supra-vaginal hysterectomy, double salpingo-oophorectomy and appendectomy for extensive chronic pelvic inflammatory disease, small uterine myomata and chronic appendicitis. Here again the gross examination presented no unusual features except that the exudate within the tubes was described as "chocolate colored and gelatinous." Both tubes showed closed fimbriated extremities.

Microscopically, the chief point of interest was the fact that in the ampullary portion of the tube there was a lining of what was unmistakably endometrium. (Fig. 4.) Sections nearer to the tube showed a characteristically tubal mucosa.

In the annular area of endometrium the tube was moderately distended. The endometrial tissue was in many places flattened out, but in most areas it showed the characteristic endometrial stroma. Here and there the endometrium was heaped up in small polypoid excrescences, showing the characteristic uterine gland pattern. The epithelium here was of the uterine type. In other places there was an adenomyo-
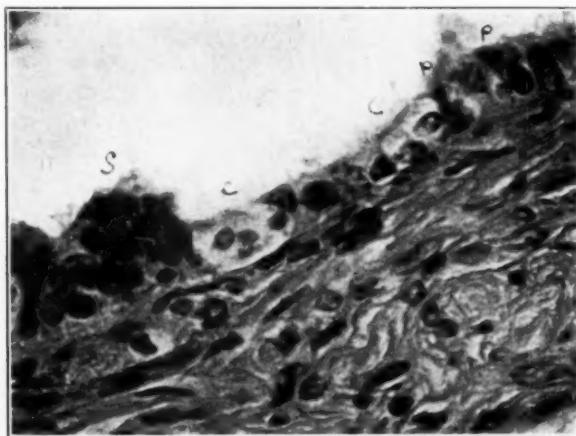

Fig. 5.—High power of wall of a tubal invagination from Case 2, showing characteristic tubal epithelium, without stroma, although derived from the uterine mucosa covering the surface. (C) ciliated cells; (S) secretory cells; (P) peg-cells.

matous invasion of the underlying muscularis, exactly like that seen in uterine adenomyoma.

Some of these invaginations exhibited an abundance of typical endometrial stroma, others showed gland-like patterns without stroma. In some of the latter, although they were obviously offshoots of the endometrium on the surface, the epithelium had again reverted to the tubal variety, with its characteristic cell types. (Fig. 5.) In other words, the normal surface mucosa of the tube had been replaced by endometrium, while in the deeper invaginations, on the other hand, the epithelium had reverted to the tubal type.

The first of these two cases is of interest, first of all, as showing that the abnormal islands of endometrium participate in menstruation and menstrual bleeding. Does not such an occurrence explain the occasional case of hematosalpinx, with perhaps intraabdominal bleeding, in which histologic examination fails to show any evidence of pregnancy? Not much endometrium would be required to produce considerable bleeding, and it could be readily overlooked except through the careful examina-

tion of many sections from all parts of the tube. Such cases have been reported by a number of authors (Meyer,[4] Neumann[5]). In some of these the histories showed that the patient had suffered with lower abdominal cramps at the menstrual periods for some time before coming to operation.

The other possibility which suggests itself in such cases is that the abnormal endometrial areas would strongly predispose to tubal implantation of the egg, as was suggested many years ago by Webster, long before the days of careful routine histologic examinations. This is a logical assumption, although this factor in tubal pregnancy is, from a numerical standpoint, probably a negligible one.

On the other hand, when one considers the interconvertibility, using this term loosely, of tubal epithelium into endometrium, it is not difficult to believe that the former may in some cases possess a physiologic receptiveness to implantation, or that it may, in other words, actually represent an intermediate type of tissue, anatomically tubal but physiologically possessing certain endometrial characteristics. This is perhaps another way of restating the old hypothesis of Webster. In some cases of tubal pregnancy which I have studied, the tubal mucosa immediately adjacent to the implantation area is strongly suggestive of endometrium.

The second case is of even greater interest from the standpoint of the subject of this paper. Here we have to deal with a segment of tube entirely lined by endometrium of a very frank type. The mucosa has, however, penetrated into the underlying muscularis, in exactly the same way as it does into the uterine muscularis in cases of uterine myoma, so that we are justified in applying the designation of adenomyoma to the tubal lesion as well. (Fig. 4.) Of especial interest, however, is the fact that some of the deeper invaginations, obviously continuous as they are with the surface, are lined by an epithelium which is of the characteristic tubal variety, and that the stroma has disappeared. (Fig. 5.)

This case is only one of a considerable group observed in our laboratory in which such intermutability of tubal and endometrial epithelium has been noted. A series of these cases was fully described by Everett[6] in a paper published last year. In this connection also, I have been much interested in the recently published studies of Allen[7] upon the changes observed in the growth of endometrial tissue implanted in the anterior chamber of the eye in rabbits. Of especial pertinence is his statement that ''in several instances the proliferated epithelium revealed many characteristics of tubal epithelium; namely, marked ciliation of all cells and the appearance of definite secretion granules.''

In the case described above, we have illustrated what I believe to be a surface transformation of tubal mucosa to endometrium, and a reversion in the deeper islands, of endometrium to tubal mucosa. This picture impresses me as a striking illustration of the intermutability of these two tissues. Furthermore it emphasizes the hazard of ascribing a tubal

origin to aberrant mucosa merely because it resembles tubal mucosa morphologically. I shall have occasion, however, to stress this point again later in this paper.

SOME DIFFERENTIATION ANOMALIES IN THE OVARY

Of all the genital epithelia the one least removed from the coelomic epithelium, from the standpoint of differentiation, is the germinal epithelium of the ovary. This would at once suggest that this tissue must retain a high degree of differentiating potency, and I believe that this is borne out by the great frequency of differentiation anomalies encountered in the ovary. Under the influence of such stimuli as inflammation, simple morphologic changes in the germinal epithelium are very
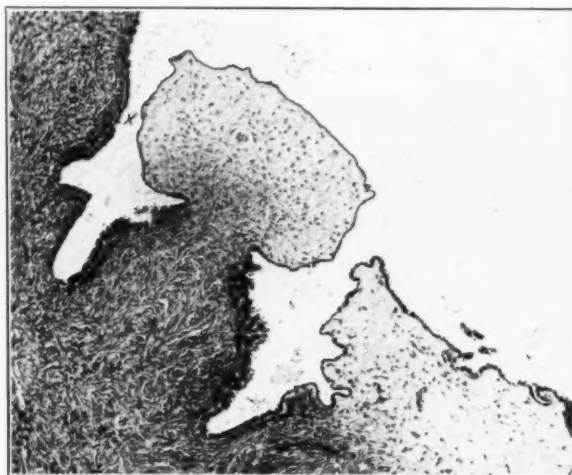

Fig. 6.—Low power of the benign serous papillomatous cystadenoma of ovary, from which, at X, the high power picture shown in Fig. 7 is taken.

frequent, so that it often becomes very tall and columnar. That it possesses a tendency to push into the ovarian stroma, even in the absence of inflammation, is not surprising in view of the early oophorogenic history of the ovary. For example, the ovaries, especially of women at middle life, frequently exhibit deep invaginations of this tissue, some of which may be cut off from the surface, with the production of the so-called germinal inclusion cysts. In such invaginations and cysts one often finds that the epithelium exhibits tubal characteristics, with ciliated, nonciliated and peg cells in varying proportions. Similar epithelial changes are seen in the surface papillomas not rarely encountered, and sometimes designated as fibroadenoma of the ovary.

From the latter one can, if a large material is examined, detect all grades of transition to the so-called serous papillomatous cystadenoma, so that the germinal epithelium origin of the latter type of ovarian cyst, unlike the pseudomucinous variety, seems to me to be thoroughly estab-

lished. It is therefore of interest to note that in the benign serous cysts the lining epithelium is often of a type exactly resembling the normal epithelium of the tube, with exactly the same types of cells, already described above (Figs. 6 and 7). Indeed, ciliation in such cysts is so common that the group is, by some of the German authors, designated "cystadenoma serosum cilio-epitheliale." Such tubal epithelium is of course not constant, and most often is found in patches of irregular size, though in some cysts it may be widely distributed. The point to stress, however, as indicating the intermutability of muellerian epithelium, is that in this ovarian tumor, obviously of germinal epithelium origin, we

Fig. 7.—High power from area X in Fig. 6. The cyst-wall here, and in many other places, is lined by an epithelium which cannot be distinguished from normal tubal epithelium. Note the (C) ciliated and (S) secretory cells, just as in the section of tube shown in Fig. 2. Such findings strongly indicate the muellerian (germinal epithelium) origin of this type of cyst.

see often a type of epithelium indistinguishable from that normally found in the tube.

Of greater interest, however, is the frequent occurrence in the ovary of endometrium indistinguishable from that seen in the uterus. The discussion as to the etiology and histogenesis of ovarian endometriosis has as yet led to no crystallization of opinion on the subject. Only one or two points bearing on this subject need be touched upon here. In going over the material studied for this paper, I have again been struck with the fact that invading germinal epithelium, in cases where surface implantation can apparently be ruled out, often develops typical tubal or endometrial characters. As most of such invaginations are seen on the convex free surface of the ovary, the possible rôle of invading tubal fimbriae does not need to be considered.

Fig. 8, for example, shows such a germinal epithelium invasion of the ovary beneath adhesions on the convex surface of the ovary. Certainly such a picture would be considered in the category of endometriosis, and certainly metaplasia, presumably the result of inflammation, would offer the logical explanation, rather than the implantation theory of Sampson. Such pictures are not rare in the ovaries, and often transitions are seen between such processes as shown in Fig. 8, and the franker types of endometriosis, with hemorrhage and perhaps endometrial cyst formation. Indeed, one finds many variations in the lining epithelium, which may be tubal or uterine in type, may or may not show an ac-

Fig. 8.—Germinal epithelium invasion into ovary, the invading epithelium assuming uterine characteristics, with the formation of many gland-like spaces resembling uterine glands in every way. The endometrium, however, shows no sign of hemorrhagic or functional activity, but this is often true of endometrium in the ovary and elsewhere. Here we are apparently dealing with a metaplasia, presumably of inflammatory origin (note the adhesions on the surface), rather than with implantation. No other endometrium was found in this ovary.

companying stroma, may or may not show hemorrhage and pigmentation. The picture furthermore may vary in different parts of the same lesion.

Another thought-provoking picture is represented in Fig. 9. Here again we have a germinal epithelium invagination, with unmistakable transition from the normal cuboidal epithelium into a type which cannot be distinguished from that normally seen in the tube. Certainly there can be no suspicion here of either implantation or the invasion of tubal fimbriae.

Different constructions can of course be put on such pictures as those I have described in these cases, but I believe them to represent merely

different phases of differentiation.   For example, the capacity of endometrium for hemorrhagic or menstrual reaction is by no means invariable in the ovary, any more than it is in the uterus.   In the latter, as I shall describe in the next section, we frequently encounter endometrium which, while typical morphologically, is apparently incapable of
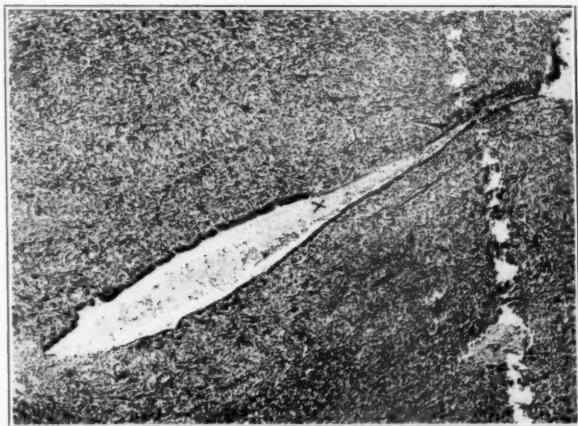

Fig. 9.—A similar cleft in the convex border of the ovary, showing direct transition (X) from the germinal epithelium to one exactly like that of the tube, with both ciliated and secretory cells.
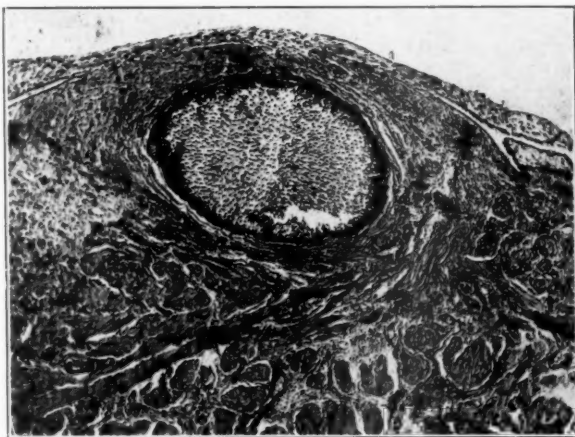

Fig. 10.—Squamous area in broad ligament near hilum of ovary. Such pictures are not rare in the serosa of the tube and at other points in the pelvic peritoneum.

the secretory or hemorrhagic response which one ordinarily associates with the endometrium.

The second point which I should like to stress is that the mere morphology of the lining cells in an area of endometriosis does not warrant drawing any conclusions as to the source of the lesion, or of the supposed "implant," as is sometimes done. For example, it would certainly not be justified to conclude that an endometrial cyst of the ovary is

derived, by implantation or otherwise, from the tubal mucosa merely because its lining epithelium is of tubal type. It would be just as proper to conclude that "tubal" epithelium in a serous cyst of the ovary arises from the tube, or to attribute a tubal origin to the areas of tubal epithelium which, as I shall show, are at times seen in the uterus.

Many other epithelial differentiation anomalies are encountered in the ovary. For example, one occasionally sees on the ovary, or for that matter, on the peritoneum of the tube or broad ligament, sharply marked off "rests" of squamous epithelium. (Fig. 10.) These have generally been assumed to be of embryonic origin, although difficult of explanation. At times, however, one can see a definite transition between peritoneum or germinal epithelium and such areas of squamous epithelium, so that it seems possible that they may in some cases, especially in the
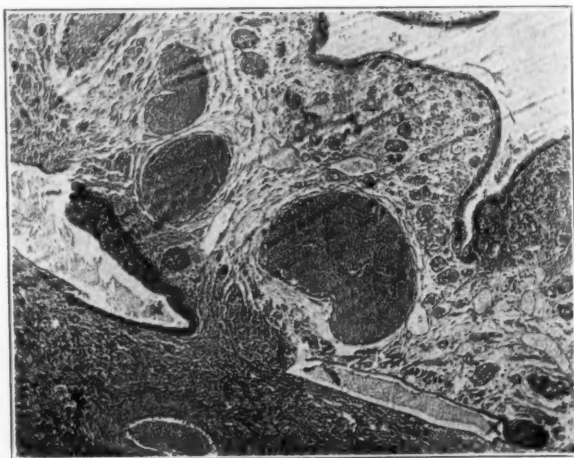

Fig. 11.—Showing apparently a direct metaplasia (X) of peritoneal endothelium, beneath fimbria ovarica, into squamous areas similar to that shown in preceding picture.

presence of inflammation, represent a metaplastic process. It is difficult to reach any other conclusion from such pictures as that shown in Fig. 11.

Anomalies of Differentiation in the Endometrium.—Squamous metaplasia of the endometrium is at times encountered, its extreme type being the so-called "ichthyosis uteri," in which the entire uterine cavity is lined by stratified squamous epithelium. There is some difference of opinion as to the explanation of this extreme type, but, at any rate, it illustrates, in an exaggerated way, the possibility of replacement of one type of genital epithelium by another. Smaller, scattered areas of squamous metaplasia are not common in the endometrium, but they are occasionally encountered, perhaps most often in cases of hyperplasia, and in certain cases of adenocarcinoma. In the case of the monkey, Streeter[9] has recently described a remarkable stratification and proliferation, almost epitheliomatous in character, at the two areas in the endome-

trium which are destined to become the sites of the double placenta of that animal.

I have, however, been especially interested in the fact that one often finds in the endometrium areas of epithelium which conform in every way to that seen in the tube. The older textbooks were in the habit of describing the uterine epithelium as of a ciliated columnar type similar to that in the tube. This description is incorrect for various reasons. In the first place, as we have already seen, the tubal epithelium itself is only partly ciliated. Secondly, ciliated cells are exceedingly sparse in the normal endometrium, and are usually not seen at all. Finally, the uterine epithelium differs very definitely from the tubal in its cell types.

The presence or absence of cilia is perhaps best studied by the fresh technic first described by Nylander. In the tube, for example, there is
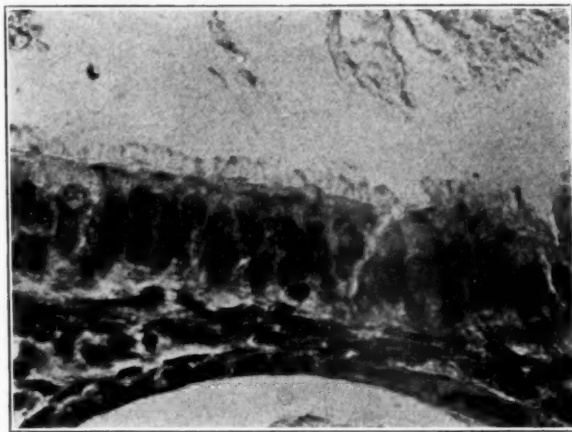

Fig. 12.—Typical tubal epithelium, with many ciliated cells, in a case of hyperplasia. Cilia are rare in the normal endometrium. With hyperplasia, however, one often finds scattered endometrial areas exactly resembling tubal epithelium, with both, or at times all three of the characteristic tubal cell types.

never any difficulty in demonstrating active and abundant ciliation by pressing out into a thin film under a cover glass, a tiny shaving or scraping of the mucosa, and examining under the higher power, without staining or fixation. By exactly the same technic I have in many cases examined the normal uterine mucosa immediately after either curetting or hysterectomy. Cilia are practically never seen, and this is confirmed by the study of fixed and stained preparations. In rare instances a few scattered ciliated cells may be noted, but they are so rare as to make one feel that they can have no functional value, and that they represent only a vestigial persistence, from a differentiating standpoint, of the ciliated epithelium higher up in the tract. In the tube the presence of cilia can of course be definitely related with function, for they undoubtedly play at least a part in the transport of the germ cells.

In studying the uterine mucosa removed by curetting, I was early

struck by the fact that in cases of hyperplasia of the endometrium cili-
ated cells, while still sparse, were more often found than in the normal
cyclical mucosa.   To put it another way, when cilia were found, the
mucosa, on subsequent microscopic examination, usually showed hyper-
plasia, and ciliated cells could often be found in the fixed and stained
sections.   Of greater interest to me, however, was the fact that in such
cases the histologic examination would not infrequently reveal areas in
which the epithelium was characteristically tubal rather than uterine in
type, an observation which so far as I know, has not been previously
made (Figs. 12 and 13).

To appreciate this distinction it must be recalled that in the normally
functioning endometrium the gland epithelium, at least, is made up of a
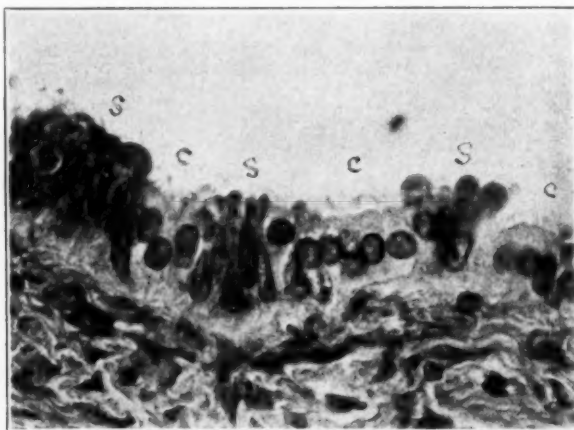uniform type of cell.   It is cuboidal or low columnar in the postmen-

Fig. 13.—Another area of tubal epithelium, showing both (*C*) ciliated and (*S*) secre-
tory cells, from a case of hyperplasia.

strual phase, becoming taller in the interval stage.   With the advent of
the secretory phase the gland epithelium of the functionalis becomes
lower, takes a pale stain, and later assumes the low, frayed appearance
characteristic of the pregravid phase.   In contrast to the glandular
epithelium, that on the surface remains tall and nonsecretory, and, even
in the normal endometrium, it may at times be very reminiscent of the
tubal epithelium.

In cases of hyperplasia the glandular epithelium is always of the non-
secretory type, and not infrequently in scattered areas one finds an ap-
pearance exactly similar to that seen in the tubes.   The two chief types
of tubal cell, the ciliated and the nonciliated, are clearly distinguishable,
while peg-cells are not infrequent.   The demonstration of such areas in
the stained section obviously explains the not-infrequent finding of cilia
in fresh preparations, as previously mentioned.   Since hyperplasia is a
condition of admittedly endocrine causation, one would naturally think

that such anomalies of differentiation might be explained on this basis. The immediate cause of hyperplasia is believed to be a relative excess of folliculin, with an absence of progestin, while there is evidence to indicate that the underlying disturbance is to be attributed to the anterior hypophysis. It is idle to speculate on the mechanism of these differentiation anomalies except on this broad basis, but that they occur admits of no doubt.

It appears, therefore, that one may find in the endometrium areas of characteristic tubal epithelium, just as characteristic endometrium may be found in the tube or in the ovary. It need scarcely be added that the abnormal areas in the endometrium, like those in the tube, are usually

Fig. 14.—Showing the "stratum reaction" of endometrium, here seen in the progravid phase. Notice the striking difference between the reaction in the middle of the glands (spongiosa) and that in the tips (basalis). The latter is seen best in the basal gland running parallel with the surface, as is so often the case. The epithelium here is nonsecretory, while that in the same gland, nearer to the surface, reacts strikingly to the selective secretory effect of progestin.

small and scattered, and that this change is not of course to be considered as constant in all cases of hyperplasia, for such is certainly not the case. The localized nature of these areas lends support to the view urged by Meyer that only certain persisting cells of indifferent nature retain this capacity for later abnormal differentiation.

There is one other interesting characteristic of uterine epithelium which deserves mention. I refer to the variations in response to physiologic stimuli which are exhibited by the epithelium of the uterine glands, or, for that matter, of any one gland, at different levels of the endometrium. I have called attention to this phenomenon in a previous paper,[10] under the designation of the "stratum reaction" of the endometrium.

If, for example, any one uterine gland in an endometrium of the pro-gravid stage is traced from its mouth down to its tip, which dips into the musculature, a very striking difference of reaction, to what is pre-sumably a uniform physiologic stimulus, may be observed.   To take the two extremes, the low mucoid appearance in the spongiosa is in sharp contrast with the sharply stained, nonsecretory epithelium of the tip of the gland in the basal stratum (Fig. 14).   Why is the epithelium in one stratum so sensitive to the progestin influence, while that in the basalis is apparently totally unresponsive?

This simple observation, it seems to me, is of profound significance as applied to the whole problem of endocrine physiology.   In studying the effects of endocrines we are prone to explain varying effects on the basis of variations in the character and dosage of the hormone administered, without regard to the varying responsiveness of the recipient tissues.   In the endometrium, for example, it is quite probable that no amount of progestin would bring about a secretory picture in the basalis, while the functionalis is readily enough influenced.

Innumerable instances of similar variations in tissues presumably of the same histologic structure might be adduced from other organs.   Note the varying responsiveness of the ovarian follicles to the same stimulus. For example, in pregnancy, some atretic follicles show extensive theca-lutein change, others none at all.   The same is true with hydatidiform mole or chorionepithelioma.   For that matter, how can we explain why, of many follicles of about the same histologic phase, only one is re-sponsive in fullest fashion to the cyclic stimuli, so that it alone among all its fellows takes the full charge, reaches full maturation and assumes the ovulatory rôle for that particular cycle?   With the same stimulus, why is it that many follicles do not ovulate each month?   The answer to these questions is far beyond our ken as yet, but on a broad basis it must be explained by the fact that tissues of the same histologic appearance and derivation differ markedly in their physiologic receptiveness to the same stimuli.

To return to the endometrium, a logical explanation for the stratum reactions would seem to be the age and maturity of the tissues in ques-tion.   For example, the glands grow in a direction away from their tips, so that the basal endometrium may be assumed to be of a less mature type than that in the upper strata.   Perhaps this developmental im-maturity is a sufficient explanation of the unresponsiveness to at least the progestin influence, although the cells are responsive to the growth-provoking influence of folliculin.

Whatever the explanation, the fact remains that not all endometrial tissue exhibits the physiologic responses which we ordinarily associate with that tissue.   In adenomyoma of the uterus, the aberrant uterine mucosa deep in the uterine wall may, or may not, menstruate.   The same is true of the endometrium in uterine polyps.   Even more striking are the variations in reaction exhibited by uterine mucosa in the ovary or

elsewhere in the pelvis, in cases of endometriosis. Frequently such ectopic tissue gives abundant evidence of physiologic responsiveness through the presence of menstrual blood, or, for that matter, through the histologic demonstration of the menstrual phases in the endometrium. Perhaps side by side with such areas, however, are others, just as definitely endometrial, which are untouched by the cyclical wave passing over them. I have already, in a previous paragraph, called attention to other variations in this ectopic endometrium, such, for example, as the presence or absence of surrounding endometrial stroma.
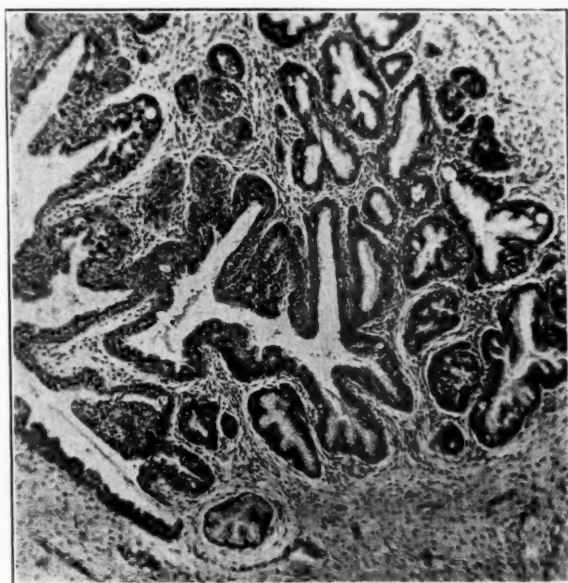

Fig. 15.—A common picture in chronic inflammation of the cervix and in cervical polyps, showing replacement of tall cervical epithelium by a stratified squamous epithelium. The possibility and great frequency of this process should always be borne in mind in the differential diagnosis of cancer, although in most cases, the distinction is not difficult.

DIFFERENTIATION ANOMALIES IN CERVIX

In this connection the anomaly which at once comes to mind is the frequent replacement of the normal high, cylindrical secreting epithelium of the cervix by a stratified squamous epithelium. This is especially frequent, of course, in connection with chronic inflammation and in cervical polyps (Fig. 15). This so-called "squamous metaplasia," so important in the differential diagnosis of cancer, has been extensively studied by Meyer[11] and others, and I have discussed it at length in one or two previous papers,[12] so that it need not be stressed here. In the presence of chronic inflammation, the invasion of the basal layers of the normal stratified squamous epithelium beneath the cylindrical epithelium, and the lifting and destruction of the latter are often clearly demonstrable, so that we have to do with an invasion rather than with a genuine metaplasia. In many cervical polyps, on the other hand, with little evidence

of inflammation, areas of such squamous type are often found far removed from the normal squamous areas of the cervix, so that here we must have recourse, it seems to me, to Meyer's explanation of metaplasia originating in vestigial cells of indifferent type.

Endometrium may at times be found within the cervix, but more particularly in cases of endometriosis or adenomyoma. So far as I know, however, no one has hitherto described a tubal type of epithelium in the cervix, and yet I believe it occurs. In a number of cases of chronic inflammation of the cervix, I have found that the glands, or, more often, the glandular retention cysts, are lined by an epithelium which is certainly not of the usual cervical type, but which histologically is indistinguishable from that found in the tubes. Such a picture is shown in
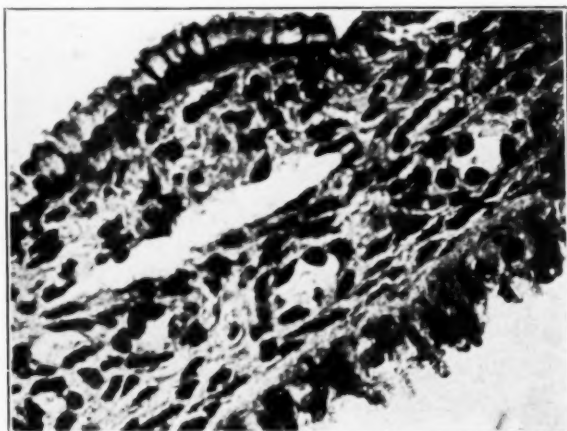

Fig. 16.—Section of cervix, showing typical cervical gland epithelium to left, while the lining of the retention cyst, seen on right, is of tubal variety, not in any way like the pressure changes often seen in the usual type of cervical retention cyst.

Fig. 16 taken from a cervical polyp, which externally is covered partly by cylindrical and partly by stratified squamous epithelium. A number of other such instances have been observed, even in the short time since I began the study of this particular question. I believe that intensive study would show them to be fairly frequent.

CAUSE OF THESE DIFFERENTIATION ANOMALIES

On the matter of explanation of these differentiation anomalies we can only speculate, chiefly because, as I have already stressed, we know so little of the underlying causes of the normal differentiation of tissues. Meyer's theory of the persistence of *anlagen* of indifferent cells would seem to offer a satisfactory explanation, if we combine with it the view that other factors must be operative to awaken the slumbering differentiating capacities of the indifferent cells. Among the secondary factors to be considered are inflammations, hyperemia, and endocrine influences. In cases of salpingitis, for example, the inflammation may be the factor which incites indifferent tubal cells to differentiate into endometrium,

and this is apparently borne out by the clinical study of such cases, as reported by Meyer, Neumann and others. Hyperemia associated with myomas, retroflexion and other such conditions may perhaps serve in the same way, while the possibility of endocrine participation is suggested, as I have already indicated, by the finding of endometrial "metaplasia" in cases of obvious endocrine disorder. It would, however, be unprofitable to pursue this subject further in the present stage of our knowledge.

SUMMARY

In this paper I have described the occurrence of certain differentiation anomalies in the epithelium of the various segments of the genital canal. Among them are the occurrence in the tube, of definite endometrial tissue; the occurrence in the ovary of either an endometrial or tubal type of tissue, and even, on the ovarian surface, of stratified squamous areas; the occurrence in the endometrium of either squamous areas or of patches of tubal epithelium; and, finally the frequent presence in the normally columnar cell regions of the cervix of stratified squamous "metaplasia" and the occasional presence of a tubal type of epithelium.

Such anomalies illustrate the tendency toward intermutability of these genital epithelia under certain conditions, a tendency obviously dependent upon their common origin from the same mother tissue, the coelomic epithelium. Cognizance of this fundamental fact must be taken in the interpretation of many pathologic lesions, such as endometriosis. In the latter, direct transformation of germinal epithelium into either a tubal or an endometrial type can be demonstrated histologically, so that it seems unnecessary to invoke the doctrine of implantation in explaining this lesion. All types of differentiation transitions may be seen in ovarian endometriosis, that is, a tubal epithelium with or without stroma, a uterine epithelium with or without glands and with or without stroma, an endometrium with or without physiologic reactivity, with or without hemorrhage.

Among other things, the study of these ovarian epithelia lends strong support to the germinal epithelium origin of serous cystadenomas, for they are often lined by epithelium indistinguishable from that of the tube. The application of such studies to the problem of tubal pregnancy is also discussed in the paper.

REFERENCES

(1) *Fischel:* Wien. Klin. Wchnschr. **35**: 355, 1922.   (2) *Meyer:* Ztschr. f. Geburtsh. u. Gynäk. **71**: 221, 1912.   (3) *Novak and Everett:* AM. J. OBST. & GYNEC. **16**: 499, 1928.   (4) *Meyer:* Zentralbl. f. Gynäk. **51**: 1482, 1927.   (5) *Neumann:* Ztschr. f. Geburtsh. u. Gynäk. **95**: 437, 1927.   (6) *Everett:* AM. J. OBST. & GYNEC. **22**: 1, 1931.   (7) *Allen:* AM. J. OBST. & GYNEC. **23**: 343, 1932.   (8) *Sampson:* Arch. Surg. **4**: 451, 1922; AM. J. OBST. & GYNEC. **4**: 451, 1922; Surg. Gynec. Obst. **38**: 287, 1924.   (9) *Streeter:* Personal Communication (to be published).   (10) *Novak:* AM. J. OBST. & GYNEC. **12**: 484, 1926.   (11) *Meyer:* Arch. f. Gynäk. **91**: 579, 1910.   (12) *Novak:* AM. J. OBST. & GYNEC. **18**: 449, 1929.

26 EAST PRESTON STREET.

THE INFLUENCE OF SEX HORMONES ON THE RETICULO-ENDOTHELIAL CELLS OF THE UTERUS AND A POSSIBLE APPLICATION TO THE TREATMENT OF PELVIC INFLAMMATORY CONDITIONS*

C. F. FLUHMANN, M.D.

SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology, Stanford University School of Medicine)

THE importance of the reticuloendothelial system for the defense of the body against infection has been repeatedly emphasized during the past few years, and the demonstration of these cells in the human uterus and appendages has drawn attention to the fact that they must play a vital rôle in pelvic inflammation. In a previous communication (Fluhmann[1]) a method was described by which certain phases of this problem could be studied experimentally and the occurrence of large numbers of tissue macrophages in the pregnant rabbit's uterus was demonstrated. The present report deals with an attempt to determine the influence of various hormonal conditions on the presence and activity of these cells in the rabbit's uterus and to discuss the possible application of the results to certain clinical problems.

EXPERIMENTAL PROCEDURE

The rabbit was chosen as the experimental animal for this work not only because of previous experience but also because it presented two very desirable features. In the first place, since the rabbit does not undergo a spontaneous estrual cycle it was a comparatively easy matter to determine the dominant effect of either ovarian hormone on the uterus at any given time. Secondly, the acute staining with trypan blue called for an animal in which repeated intravenous injections could be given over a period of a few days. The rabbits were purchased on the open market, so that age and previous history were unknown, but an attempt was made not to use does which had had previous litters and to limit them as much as possible to weights varying between 1.5 and 2.5 kilos.

As in the previous study, the macrophages were demonstrated by means of intravital staining. Each rabbit received a total of from 20 to 25 c.c. per kilo body weight, of a one per cent aqueous solution of trypan blue, administered in from 4 to 9 intravenous injections over a period of three days. This procedure resulted in a heavy mortality, but except for a few rabbits in which the macrophages were numerous and easily demonstrated the present report is based on animals surviving and completely stained. They were sacrificed the day after the last injection. The uteri were fixed in formalin, and paraffin sections were made using alum carmine as the counterstain.

The various hormonal conditions studied in these experiments are so generally

recognized at the present time that a mere mention of them should suffice. The spayed animals of course represent a total absence of all hormonal stimulus to the uterus. The normal unmated rabbit presents a uterus in the estrin phase since the ovaries of these animals contain graafian follicles and no active corpora lutea. The same condition was also reproduced in the spayed rabbit by the administration of urine from pregnant women or of theelin, and it could be intensified in normal animals by giving large doses of theelin. Since no progestin, the specific hormone of the corpus luteum, was available for this work, the same effect was obtained by inducing a luteinization of the rabbit's ovaries and this in turn produced the progestin which stimulated the typical progestational proliferation of the uterus. This was accomplished by the intravenous administration of pregnancy urine, but as some criticism might be advanced owing to the fact that estrin is also present in this urine, the same effect was also produced by the use of an estrin-free ovary-stimulating extract made from blood of pregnant women.

The urine was administered intravenously, the usual dose both for specimens from pregnant and nonpregnant women being from 5 to 12 c.c. once or twice daily. The preparation of theelin employed was labelled as containing 50 rat units per cubic centimeter, and in all cases the dose was 0.5 or 1.0 c.c. twice daily. This preparation was given intravenously in a few instances, but intramuscular injections were substituted as this seemed to be more effective.

The method of preparing an ''estrin-free ovary-stimulating extract'' from the blood of pregnant women is one developed in connection with other studies (Fluhmann[2]) and is known in the laboratory as ''Procedure B 118.'' The blood was obtained by venipuncture and placed in a container with crystals of sodium citrate. This was centrifuged, the cells discarded, and the clear blood plasma extracted five times with ether. Six volumes of 95 per cent ethyl alcohol were then added to the plasma, and the resultant precipitate obtained by centrifugalization was washed twice with ether, dried, ground up in a mortar, and extracted overnight with 20 to 30 c.c. of a sodium acetate-acetic acid buffer having a P_H of about 4.4. This solution was then centrifuged and treated by adding 10 volumes of 95 per cent alcohol. The resultant precipitate was washed with ether and dried. It was a clear white powder, readily soluble in saline or the buffer solution. This preparation was usually made up for injection so that 1 c.c. of the extract was equivalent to 2.3 c.c. of the original blood plasma.

A total of 89 rabbits survived the various experimental procedures and are available for study. They may be divided into two main groups, namely, (A) animals representing the occurrence of macrophages in the rabbit's uterus under various hormonal conditions, and (B) animals under similar conditions, but in which an injury to the uterus was performed in order to determine the response of macrophages to this stimulus. Each of these two groups is again subdivided into three categories according to the existing hormonal condition of the uterus, namely, (a) postcastration atrophy, (b) estrin phase, and (c) progestin phase.

A.—1. *Postcastration Atrophy.*—Five spayed rabbits were injected with trypan blue in order to determine the presence of macrophages in the absence of all ovarian stimulation. The castration had been performed from one week to three months prior to the experiment.

2. *Estrin Phase.*—Thirty-one rabbits in which the uterus was under the influence of the ovarian hormone *estrin*, were stained with trypan blue. These, again, are represented by 6 groups:

a. Normal unmated animals (5 rabbits).

b. Normal unmated animals given a series of intravenous injections of urine from nonpregnant women. A total of from 26 to 56 c.c. of urine was given, and they were sacrificed at various times from the fifth to the eleventh day following the first injection (9 rabbits).

c. Normal females given intravenous injections of urine from pregnant women, but in which the progestational proliferation failed to occur and the uterus remained in the estrin phase. Two animals received 20 c.c. of urine and were sacrificed on the fourth day, while the third received 56 c.c. and was autopsied on the tenth day after the first injection (3 rabbits).

d. Spayed rabbits administered theelin. One received 750 rat units intravenously and was sacrificed on the seventh day. One was given 312 units intramuscularly and killed on the tenth day, while two received 500 units and were killed on the sixth and tenth days respectively (4 rabbits).

e. Spayed rabbits given intravenous injections of urine from pregnant women. A total of 40 c.c. was given each animal and they were sacrificed on the eighth day (3 rabbits).

f. Normal animals given theelin. Two animals received 800 and 900 rat units intravenously and were killed on the ninth and eighth days respectively. Two were given 800 units intramuscularly and were sacrificed on the tenth day, two received 400 units and were killed on the fifth day, while one had 850 units and was killed on the ninth day (7 rabbits).

3. *Progestin Phase.*—Nineteen rabbits were used in which a progestational proliferation of the uterus was induced by the administration of urine from pregnant women. The total amount of urine used varied from 26 to 60 c.c. and was given in daily intravenous injections over a period of from three to seven days. The experiments were also completed at various times so that uteri were obtained representing the changes that occurred from the third to the tenth day after the first injection. In four instances the rabbits received 82 c.c. and were sacrificed on the fourteenth day so that the changes present when regression takes place could also be studied.

B.—In the second group of experiments essentially the same conditions prevailed as in the first group, but in addition a traumatic injury to the uterus was performed. This procedure was based on the method of Long and Evans for the production of artificial placentomas in rats and consisted in making a small incision in the lower abdomen of the anesthetized (ether) animal, drawing out one of the uterine horns and inserting a small black silk ligature. The cornu was then dropped back into the pelvis, and the wound was closed by a linen figure-of-eight stitch in the muscle and metal clips for the skin. The operation was generally done the day before the intravital staining was begun so that in all cases the uteri represent the changes found on the fourth or fifth day following the traumatization. A total of 34 rabbits was employed, and this series of experiments may also be subdivided according to the existing hormonal condition, as follows:

1. *Postcastration* (4 rabbits).

2. *Estrin Phase.*—

a. Normal unmated animals (6 rabbits).

b. Animals given pregnancy urine but in which progestational proliferation failed to occur. Four of the rabbits received 12 c.c. of urine, and one 20 c.c. Two were killed on the eighth and one on the ninth day following the first injection (5 rabbits).

c. Normal unmated animals given theelin. One received 400, one 450, and seven 500 units of theelin intramuscularly. Two died on the fourth and seven were sacrificed on the fifth day after the first injection (9 rabbits).

3. *Progestin Phase.*—

a. Animals given pregnancy urine. One rabbit received 12 c.c., five 20 c.c., and one 23 c.c. of urine. One was killed on the seventh, one on the tenth, and the rest on the eighth day after the first injection (7 rabbits).

b. Animals given intravenous injections of an estrin-free ovary-stimulating blood extract (B 118). All received 1 c.c. on one day, and 0.5 c.c. the following morning. They were sacrificed on the seventh day after the first injection (3 rabbits).

RESULTS

The macrophages are readily recognized by the blue color of the dye particles which they have phagocytized, but since in some animals polymorphonuclear leucocytes also took up the trypan blue, every section was studied under high magnification in order to be assured of the exact nature of the vitally stained cells.   Tissue macrophages show considerable individual variation as to size and shape, but generally range from 15 to 30 micra in diameter and present a round or oval outline, although they may be spindle-shaped, elongated, or may branch in one or more directions (Fig. 1).   The nucleus is usually round or oval but often kidney-shaped, and is invariably situated at the periphery of the cell.
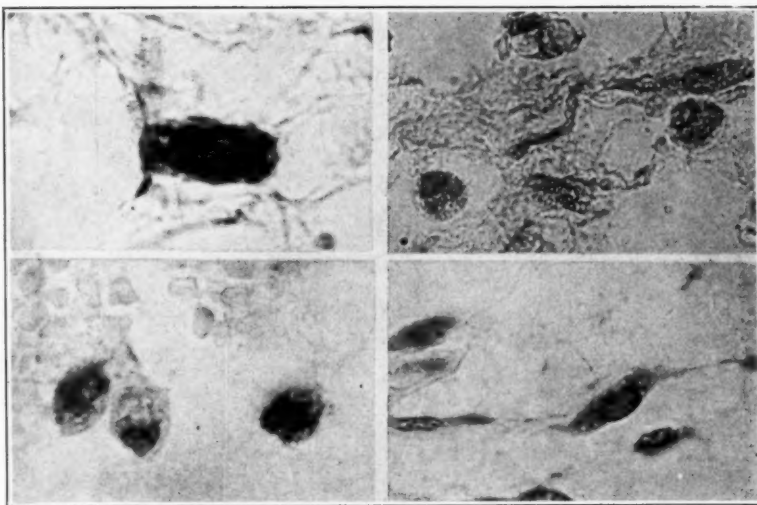

Fig. 1.—Photomicrographs showing various types of macrophages occurring in the wall of the rabbit's uterus (oil immersion magnification).

The cytoplasm is finely granular, vacuolated, and large and small particles of the dye or other phagocytized material are irregularly distributed throughout.

In estimating the intensity of macrophage response in the uteri of the animals, three points have been especially considered. In the first place, the total number of cells present was noted, and in some instances counts were made of the number found in 100 oil immersion fields.   Secondly, the distribution of the macrophages proved to be of importance, since usually they are only found in the propria mucosae but under certain conditions they may appear in the lymph spaces of the muscular layers. And thirdly, attention was directed to the intensity with which the cells were stained.   On the basis of these three points it was found convenient to grade the reactions in the different specimens into five groups, denoted as 0, +, ++, +++, and ++++.

GROUP A EXPERIMENTS

1. *Postcastration.*—The uteri of the spayed rabbits had undergone an extensive atrophy of both mucosal and muscular layers (Fig. 2), and a careful search through many sections showed that macrophages were completely absent.

2. *Estrin Phase.*—Since ovulation does not usually occur spontaneously in the rabbit, the ovaries of the normal unmated doe show the presence of mature graafian
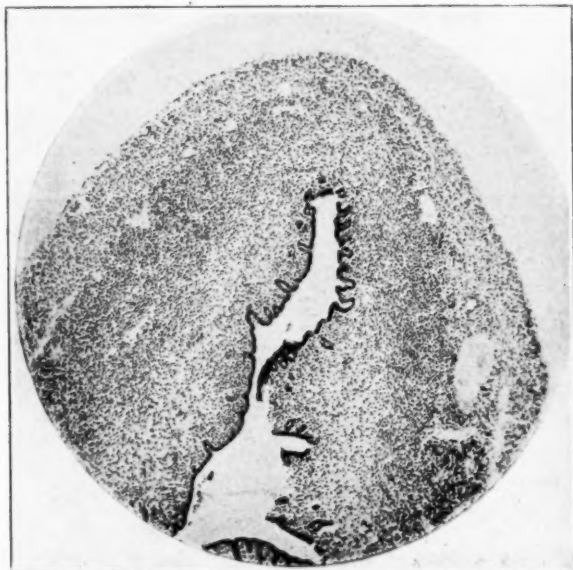

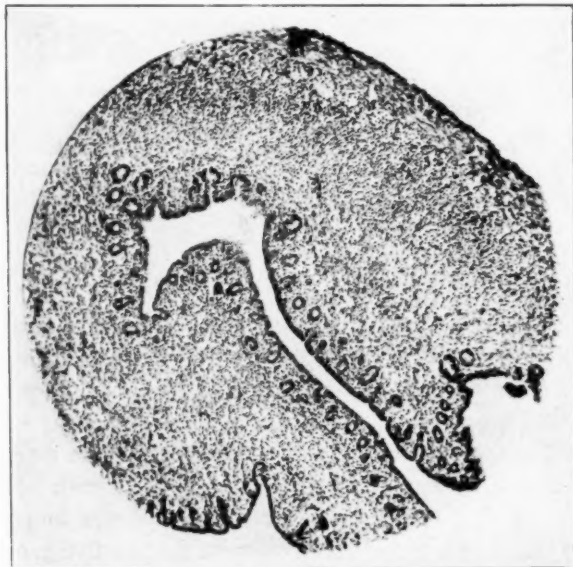Fig. 2.—Atrophied uterus of a spayed rabbit (low power).

Fig. 3.—Rabbit's uterus in estrin phase (low power).

follicles and the uterus is under the influence of the ovarian follicular hormone (Fig. 3). This condition was represented in this series by three groups of animals, namely, 5 normal females given no treatment except the intravital staining, 9 which received a series of intravenous injections of urine from nonpregnant women, and 3 given injections of pregnancy urine but the progestational proliferation failed to occur and the uterus remained in the estrin phase. The search for macrophages in this group revealed the fact that very few stained cells are usually present, although a slight increase was noted in some of the older heavier animals which had previously had litters. In 7 instances there was a total absence of macrophages (0), in 6 only an occasional cell could be found (+), while in 3 there was a sufficient number present to cite as ++. One large female weighing 3 kilos showed many cells and was estimated as +++ to ++++. The distribution of the cells was
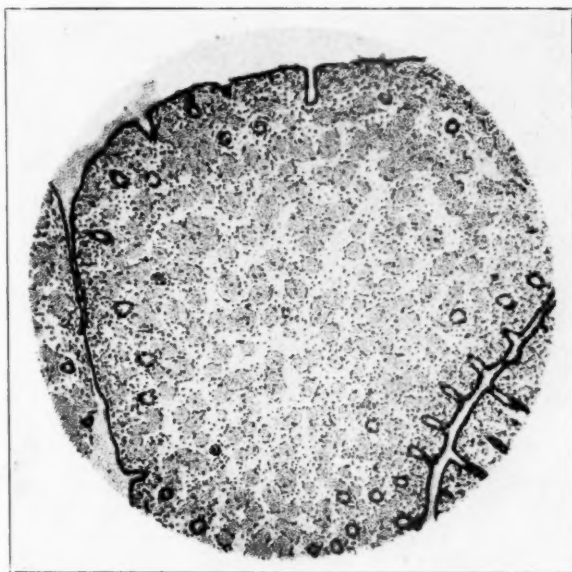

Fig. 4.—Growth of blood vessels in the propria mucosae of the rabbit's uterus induced by the administration of large doses of theelin (low power).

limited, and they were found almost exclusively in the deeper layers of the propria mucosae.

A somewhat different result was noted in the animals administered theelin in spite of the fact that the uterus still had the histologic characteristics of the estrin phase. The uteri of the castrated rabbits which received theelin or pregnancy urine showed that a *restitutio ad integrum* had taken place. The mucosa had developed from a shrunken atrophied structure to its normal state, and associated with this growth large number of macrophages (++ to +++) appeared. This was noted in 5 out of 7 instances. On the other hand, the administration of theelin to normal animals resulted in a marked increase in the number of macrophages (++ to +++) in only 2 instances, while in 3 there was possibly a slight increase (+ to ++), and in 2 there was no noticeable response. Of importance in this group was the evidence of growth in the mucosa, and an accompanying tremendous development of the blood vessels of the propria mucosae (Fig. 4).

3. *Progestin Phase.*—Nineteen specimens are available from animals given injections of urine from pregnant women, which may be considered as essentially

a mixture of estrin and ovary-stimulating hormones (Prolan). The uteri in all cases showed the progestational proliferation of the mucosa with its characteristic treelike development (Fig. 5), which is associated with the formation of corpora lutea in the ovaries and is attributed to the hormone *progestin*. Since the specimens were obtained at various times from three to fourteen days after the first injection of urine they represent various stages of proliferation from the earliest changes to the regression which is apparent on the fourteenth day. In this case, the macrophage response proved inconstant. In 6 instances there was an increase in the number of the cells (++ to +++), in 3 there was a doubtful reaction (++), while in 10 no increase in the number of cells could be demonstrated.

The experiments of this group thus demonstrated the total absence of macrophages in the uteri of spayed animals and their infrequency in normal unmated female rabbits. It was also shown that although a definite macrophage response appeared
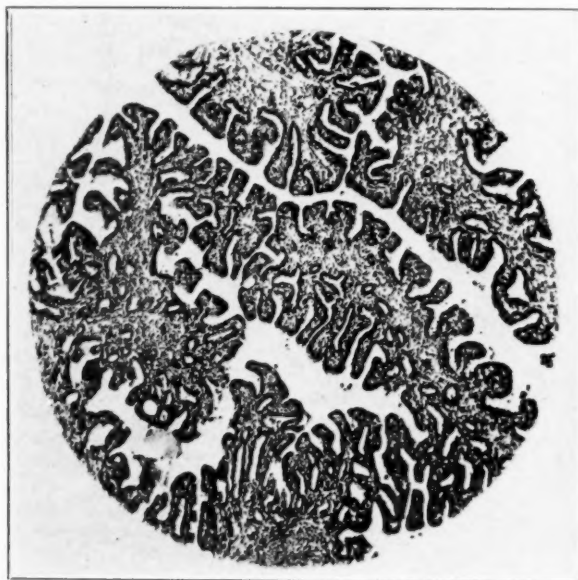
Fig. 5.—Progestational proliferation of rabbit's uterus (low power).

in the atrophied uteri of the castrates when stimulated to growth, it was not possible to consistently effect an increase in the normal animals either by giving large doses of theelin or by inducing the progestational proliferation which resulted from the administration of pregnancy urine.

GROUP B EXPERIMENTS

The object of this series was to determine the reaction of the uterus to trauma, and attention was directed to the macrophage response at the site of insertion of the silk ligature, at a distance from this area but in the same horn, and in the opposite untreated uterine cornu.

1. *Postcastration.*—The results of this group were of such uniformity that only 4 animals were used. In all instances a considerable number of well-stained macrophages were observed at the site of injury (+ to +++), but none could be found at any distance from this area either in the same or in the opposite uterine cornu.

2. *Estrin Phase.*—The experiments of this group are represented by 6 normal unmated rabbits and 5 rabbits given pregnancy urine but failing to develop pro-

gestational changes.   The findings were essentially the same as in the spayed group, although the macrophage response at the point of injury was more intense.   In 8 animals a ++ to +++ reaction was noted at the level of insertion of the ligature, but a ++ was noted only twice at any distance from this area.   In 6 instances no cells could be demonstrated in the opposite uterine cornu, a + was found 3 times, a ++ once, and a ++ to +++ reaction once.

A different state of affairs was now to be noted in the group of animals given large doses of theelin before and after the insertion of the silk ligature.   The characteristic marked development of blood vessels had taken place, and this could readily be seen grossly at operation when the uterus was found to be of a deep purplish-red color.   At the site of injury a local increase of macrophages (+++) was clearly demonstrated as in the previous group, but of especial interest was the widespread reaction present throughout the whole uterus.   Sections taken from the injured cornu at a distance from the point of insertion of the ligature and sections taken from the opposite untreated uterine horn revealed a widespread accumulation of deeply staining active tissue macrophages.   In 6 cases this was described as +++ and in 3 as ++.

3. *Progestin Phase.*—An effect similar to that produced by the administration of large doses of estrin was found to exist in the group of animals whose uteri were traumatized while they were undergoing progestational proliferation.   This was shown in 7 rabbits given pregnancy urine and in 3 which received the extract made from blood of pregnant women.   In 7 instances an intense response (+++ to ++++) occurred at the site of injury while in 3 it was denoted as ++, but again of importance was the marked reaction found throughout both uterine cornu.   The numbers of macrophages and the intensity of the staining in many cases closely simulated the findings during pregnancy.   At any point distant from the site of injury in either the treated or the untreated horn of the uterus were found large numbers of macrophages presenting evidence of tremendous activity as shown by the intensity of the staining, their distribution, and the development of new cell forms.   In 8 cases this was described as +++ or ++++, while it was given as ++ in two instances.

The second group of experiments thus showed that in both spayed and normal animals the insertion of a silk ligature in one of the uterine horns resulted in a fairly intense response with macrophages but this was of a purely local nature and the whole organ did not take part.   On the other hand, when the uterus was stimulated to growth by the administration of estrin or underwent the qualitative changes effected by progestin it acquired a tremendous power of responding with macrophages to a traumatic stimulus.   This was shown not only in the local accumulation of vitally stained cells at the site of injury but in their increased activity and their presence in exceedingly great numbers throughout the whole organ.

ENDOCRINES AND RETICULOENDOTHELIAL SYSTEM

Although only a few attempts have as yet been made to determine if any relationship exists between the various hormones and the reticuloendothelial system, a number of reports suggest that certain endocrinological effects are possibly associated with an increased or decreased activity of the fixed or circulating macrophages.   Saxl and Donath[3] found that posterior pituitary gland extract would prevent exudate formation and diminish the production of edema in the experimental conjunctivitis of rabbits.   They interpret this result as due to a local depression of the reticuloendothelial cells, although Tainter[4] and others have shown that

both epinephrine and posterior pituitary extract may prevent local edemas and believe that this is due merely to a reduction in the amount of blood flow to the affected area. Goldzieher and Hirschhorn[5] have shown that the storage of trypan blue may be altered by various gland preparations, and somewhat similar conclusions were reached by Leites and Riabow.[6] Mandelstamm[7] demonstrated that epinephrine has a stimulating action on the reticuloendothelial system, as seen in a rapid development of individual cells, increased phagocytosis, and the appearance of new cell-forms. On the other hand, Stephan[8] believes that the suprarenal hormones have an inhibitory influence on the reticuloendothelial system, while Willmore and Douglas[9] described a widespread degeneration of macrophages in a case of suprarenal tumor.

On the basis of the experimental findings of this study, it is impossible to determine the exact rôle of estrin and progestin in stimulating the macrophage response of the rabbit's uterus. It would seem, however, that estrin is the chief factor concerned and although there is no exact information available as to the mechanism by which this reaction is produced, three possibilities must be considered. In the first place, estrin may have the property of directly stimulating the whole reticuloendothelial system and this conception receives some support from the work of Benda[10] and Lundwall[11] who found evidence of such an increased activity during pregnancy. If this is the case it should be possible to demonstrate a heightened activity of macrophages in other areas than the pelvis, and a number of experiments are at present under way which it is hoped may throw some light on this point.

The second possibility is that estrin may be able to stimulate the production of epinephrine which in turn may be responsible for the intensification of the macrophage response, as suggested by Mandelstamm.[7] However, Dr. M. L. Tainter of the Department of Pharmacology studied this question at my request and was unable to show any marked increased output of epinephrine as demonstrated by the blood pressure record, following the intravenous injection to a cat of as much as 100 rat units of theelin. It would seem very doubtful, therefore, that this explanation is the correct one.

The third possibility was mentioned in the preliminary report of this work (Fluhmann[12]), and would theoretically appear to be the most logical, namely, that the increased macrophage activity is the direct result of the intense tissue growth set up in the uterus by the ovarian hormones. Further credence is given to this conception when one considers the tremendous development of blood vessels which accompanies these changes and the close connection known to exist between the vascular channels and the macrophages. From this standpoint it would be of interest to determine if the macrophage response is increased when the uterus is stimulated to growth by nonspecific substances such as foreign proteins or histamine (Robinson and Zondek[13]).

DISCUSSION

In considering the possible practical application of this work, it is important to determine the incidence of tissue macrophages in the human pelvic organs, and fortunately there are a number of observations available on this question.   The greatest number of these cells is found during pregnancy, when they are seen throughout the uterine wall and in the broad ligament (Hornung, [14] Hofbauer,[15] Motta[16]), while they persist in the myometrium for some time during the early puerperium (Teacher[17]).   They may also be readily observed in areas of degeneration in fibromyomata during pregnancy (Fig. 6).   Motta[16] has described

Fig. 6.—Macrophages from a fibromyoma uteri removed during pregnancy (oil immersion magnification).

phagocytic cells consistently present in the connective tissues of the nonpregnant uterus and stated that they greatly increased in number at the time of the menstrual period.   Richter[18] studied the presence of reticuloendothelial cells in the female genital organs and believed that they are of an insufficient number to be of practical importance, but it must be noted that his patients were older women varying from forty-nine to sixty-six years of age.   The occurrence of tissue macrophages in some cases of salpingitis has been mentioned by Mallory,[19] although no detailed study of this question seems to have been made.   It may be said, however, that their implication in these cases is a variable factor, but in some instances they may be demonstrated in large numbers throughout the tubal wall and in the exudate (Fig. 7).   Macrophages are also at times seen in the stroma of hyperplastic endometrium, and

a similar, if not identical, type of cell often occurs in the lumina of the endometrial glands (Fluhmann[20]). It may thus be concluded that tissue macrophages *do* occur in the human pelvic organs, and it is also of interest that they have been found chiefly at times when the ovarian hormones exert their greatest influence, while they were few in number in the senile individuals studied by Richter.

The important rôle of the reticuloendothelial system in infection as well as in general and local immunity is now generally recognized, and space does not permit a detailed analysis of this aspect of the problem. The studies of Metschnikoff, Marchand and Maximov are well known,
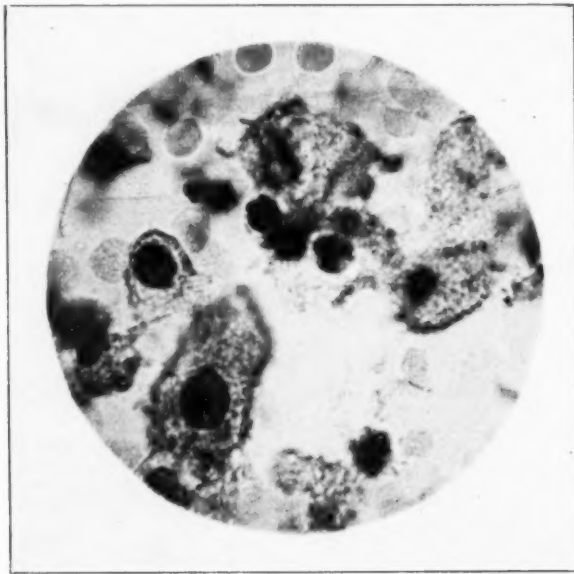
Fig. 7.—Macrophages in the exudate of a subacute salpingitis (oil immersion magnification).

and a number of valuable reviews have recently been published by Sacks,[21] Jaffé[22, 23] and Gay.[24] It may be said briefly, however, that "the following functions have been attributed to the reticuloendothelial cells in connection with infections: first, the phagocytosis and intracellular destruction of the microorganisms; second, the reception, detoxication and digestion of the waste products that are formed during the process of inflammation, including the toxic substances liberated from the bacteria; third, the absorption of soluble toxins; and fourth, the secretion of the antibodies" (Jaffé[22]).

It is readily seen that any factor which may stimulate the local reaction of reticuloendothelial cells is of vital importance in combating a local or general infection. This has been demonstrated in many ways. Gay and Morrison[25] by stimulating a macrophage response in the pleura

of experimental animals induced a condition which enabled them to survive infections normally rapidly fatal. Nakahara[26] produced a macrophage reaction in the peritoneal cavity of mice and found that as a result they would survive multiples of the fatal doses of streptococci and pneumococci. A closely related phenomenon has been accomplished many times and in various ways in inducing a local skin immunity by Besredka,[27] Mallory and Marble[28] and others. Stuppy, Cannon and Falk[29] found an extensive local accumulation of macrophages in the lung following vaccination against Type I pneumococci. The studies of Louros and Scheyer[30] point to the increased resistance to streptococcus infection resulting from the stimulation of the reticuloendothelial system.

The main interest of these observations as applied to gynecologic problems lies in the fact that certain methods of medical therapy which have been advocated in recent years for pelvic infection have been shown to stimulate the local production of macrophages. The use of colloidal substances, and especially foreign proteins, for the treatment of pelvic inflammatory disease has been recognized for some time and this procedure has been shown by Nissen,[31] Siegmund,[32] Louros and Scheyer[30] and others to produce a stimulation of the reticuloendothelial system. A few years ago, before this Society, Polak[33] recommended the use of mild exposure to roentgen rays as a method of treating similar conditions. Although he attributed the favorable results obtained as due to the temporary amenorrhea which resulted, it is of interest to note that many observers claim that such mild x-ray treatment acts as a stimulant to the local macrophages (Schmidt,[34] Holtermann,[35] Warthin and Case,[36] Schwienhorst,[37] and others).

The marked stimulation of macrophages which has been accomplished in the present study suggests that attention should be directed to the possible use of sex hormones in the treatment of pelvic inflammatory disease. There are no doubt many difficulties to be faced at the present, especially as regards preparations and dosage to be employed, but these should not prove insurmountable. It would seem that large doses of estrin to stimulate a local hyperemia and macrophage reaction without necessitating an ovarian response might prove sufficient, but there is no clear evidence that this is practical with the preparations at present available. On the other hand, Klein,[38] Zondek,[39] and Montag[40] have reported that the use of Prolan in such patients has yielded encouraging results. They have succeeded in inducing a pelvic hyperemia and an accompanying local increase in temperature, while they observed a more rapid disappearance of pain and a shorter period of convalescence. Although an adverse report has been given by Bauer and Lehfeldt,[41] the method certainly deserves a thorough trial. The number of patients treated to date on the Stanford Gynecological Service is too small to draw conclusions from, but it is felt that as an adjunct to the usual con-

servative measures for pelvic inflammatory disease the use of sex hormones may in time prove of considerable value.

SUMMARY

A series of experiments were performed to determine the incidence of tissue macrophages in the uterus of the rabbit, as well as the macrophage response following trauma, under various hormonal conditions.

The uterus of the normal female rabbit was found to contain only a few macrophages scattered throughout the propria mucosae, while they were totally absent in the atrophied uterus of spayed animals. The injection of large doses of estrin or the induction of progestational proliferation of the rabbit's uterus by the administration of urine from pregnant women resulted in an increase in the number of macrophages in less than 50 per cent of the cases. However, the growth of the spayed rabbit's uterus which resulted from estrin stimulation was associated with the appearance of large numbers of macrophages.

The traumatization of one horn of the uterus resulted in the appearance of many macrophages at the site of injury in all animals, but in the normal doe or in the spayed animal this was of a purely local nature. In the rabbits given large doses of theelin or in which a progestational proliferation had been induced, the response was tremendously increased and was apparent not only at the site of injury but throughout the whole uterus.

It may thus be said that when the rabbit's uterus undergoes the tissue differentiation and vascular changes brought about by the ovarian hormones estrin and progestin, it acquires the power of responding much more actively with macrophages to traumatic stimuli.

The possibility of employing sex hormones in the treatment of pelvic inflammatory conditions is discussed.

REFERENCES

(1) *Fluhmann, C. F.:* AM. J. OBST. & GYNEC. **15**: 783, 1928. (2) *Idem:* Proc. Soc. Exper. Biol. & Med. **29**: 1193, 1932. (3) *Saxl, P., and Donath, F.:* Klin. Wchnschr. **4**: 1866, 1925. (4) *Tainter, M. L.:* J. Pharmacol. & Exper. Therap. **33**: 129, 1928. (5) *Goldzieher, M. A., and Hirschhorn, L.:* Arch. Path. & Lab. Med. **4**: 958, 1927. (6) *Leites, S., and Riabow, A.:* Ztschr. f. d. ges. exp. Med. **59**: 709, 1928. (7) *Mandelstamm, M.:* Virchows Arch. f. path. Anat. u. Physiol. **261**: 858, 1927. (8) *Stephan, R.:* München. med. Wchnschr. **72**: 628, 1925. (9) *Willmore, G., and Douglas, M.:* Brit. M. J. **1**: 16, 1925. (10) *Benda, R.:* Zentralbl. f. Gynäk. **50**: 727, 1926. (11) *Lundwall, K.:* Zentralbl. f. Gynäk. **50**: 2874, 1926. (12) *Fluhmann, C. F.:* Proc. Soc. Exper. Biol. & Med. **29**: 1027, 1932. (13) *Robinson, M. R., and Zondek, B.:* AM. J. OBST. & GYNEC. **8**: 83, 1924. (14) *Hornung, R.:* Zentralbl. f. Gynäk. **48**: 2170, 1924. (15) *Hofbauer, J.:* Bull. Johns Hopkins Hosp. **38**: 255, 1926. (16) *Motta, G.:* Haematologica **8**: 91, 1927. (17) *Teacher, J. H.:* J. Obst. & Gynec. Brit. Emp. **34**: 1, 1927. (18) *Richter, J.:* Monatschr. f. Geburtsh. u. Gynäk. **64**: 323, 1923. (19) *Mallory, F. B.:* The Principles of Pathologic Histology, Philadelphia, 1914, W. B. Saunders & Co., p. 601. (20) *Fluhmann, C. F.:* Surg. Gynec. Obst. **52**: 1051, 1931. (21) *Sacks, B.:* Physiol. Reviews **6**: 504, 1926. (22) *Jaffé, R. H.:* Arch. Path. & Lab. Med. **4**: 45, 1927. (23) *Idem:* Physiol. Reviews **11**: 277, 1931. (24) *Gay, F. P.:* Arch. Path. & Lab. Med. **1**: 590, 1926. (25) *Gay, F. P., and Morrison, L. F.:* J. Infect. Dis. **33**: 338, 1923. (26) *Nakahara, W.:* J. Exper. Med. **42**: 201, 1925. (27) *Besredka, A.:* Bull. de l'Inst. Pasteur **23**: 873, 1925. (28) *Mallory, T. B., and Marble, A.:* J.

Exper. Med. **42**: 465, 1925. (29) *Stuppy, O. W., Cannon, P. R., and Falk, I. S.:* Proc. Soc. Exper. Biol. & Med. **26**: 314, 1929. (30) *Louros, H., and Scheyer, H. E.:* Ztschr. f. d. ges. exp. Med. **55**: 702, 1927. (31) *Nissen, R.:* Klin. Wchnschr. **1**: 1986, 1922. (32) *Siegmund, H.:* München. med. Wchnschr. **70**: 5, 1923. (33) *Polak, J. O.:* AM. J. OBST. & GYNEC. **18**: 580, 1929. (34) *Schmidt, E. A.:* Strah lentherapie **12**: 517, 1921. (35) *Holtermann, G.:* München. med. Wchnschr. **71**: 254, 1924. (36) *Warthin, H. S., and Case, J. T.:* Am. J. Roentgenol. **12**: 102, 1924. (37) *Schwienhorst, M.:* Beitr. z. path. Anat. u. z. allg. Path. **81**: 375, 1928. (38) *Klein, P.:* Ztschr. f. Geburtsh. u. Gynäk. **95**: 371, 1929. (39) *Zondek, B.:* Die Hormone des Ovariums und des Hypophysenvorderlappens, Berlin, 1931, Julius Springer, p. 293. (40) *Montag, H.:* Monatschr. f. Geburtsh. u. Gynäk. **88**: 212, 1931. (41) *Bauer, A. W., and Lehfeldt, H.:* Zentralbl. f. Gynäk. **53**: 3404, 1929.

STANFORD UNIVERSITY HOSPITAL.

INCREASE OF GUANIDINE COMPOUNDS IN ECLAMPSIA: AN EXPERIMENTAL STUDY*

PAUL TITUS, M.D., F. C. MESSER, B.S., AND R. H. McCLELLAN, M.D., PITTSBURGH, PA.

(From the John C. Oliver Memorial Research Foundation, St. Margaret Memorial Hospital)

ROUTINE blood chemistry studies in preeclampsia and eclampsia have been disappointing, but biochemistry as a special field for the investigation of these conditions still offers immeasurable possibilities.

Studies of the behavior of the blood sugar in preeclampsia and eclampsia with which our group has been concerned[1,2,3,4,5] indicate that these toxemias have a hypoglycemic basis. We have demonstrated wide fluctuations in blood sugar during eclampsia with sudden and sharp falls in the sugar preceding the convulsions, as well as a general trend toward hypoglycemic values. These findings have recently been confirmed by others.[6,7,8]

We are now convinced that a disturbance in carbohydrate metabolism is common to all types of pregnancy toxemia, and originally believed that the basis for this was a simple deprivation or deficiency of carbohydrates, mainly dietetic in origin. It seems apparent, however, that there must be some added element which causes either a direct loss of body glycogen or else a disturbance in the normal glycogenic function of the liver or both, especially if the disturbance is to develop into such a violent clinical upheaval as an attack of eclampsia.

In a search for possible causes of such unusual metabolic findings as these blood sugar fluctuations which we have described in eclampsia Dr. H. D. Lightbody, formerly director of this laboratory, attracted our attention to the recent work of Minot and Cutler[8,9] on the association between liver injury and increase of guanidine in the blood, as well as the fact of the hypoglycemia produced by toxic doses of

guanidine and its compounds.[10, 11, 12, 13, 14, 15]   This latter phenomenon has been extensively studied in connection with the use of synthalin, a complex guanidine derivative originally developed for use in reducing blood sugar in diabetes but now abandoned because of its toxicity.

The toxic effects of this and other guanidine compounds have been investigated experimentally as well as clinically, and several interesting facts develop from this work. It is significant to discover that by over-dosage with certain guanidine compounds one may reproduce in animals practically all of the clinical features of eclampsia in the human being. These include disturbed carbohydrate metabolism, fluctuations in blood sugar, increase in blood uric acid, amino acid and lactic acid, increase in blood pressure, edema, albuminuria, muscular tremor, and a series of convulsions ending in death.

HYPERGUANIDINEMIA AND HYPOGLYCEMIA

Guanidine poisoning promptly produces a hypoglycemia, and Minot[15] has shown that the mechanism by which this occurs is a simple one. It is, namely, that this intoxication seems to interfere with oxidative processes in the tissues resulting in an accumulation of lactic acid, with a secondary rise in its concentration in the blood whereupon "much lactic acid is excreted in the urine. This accumulation and loss of lactic acid represents a serious drain on the carbohydrate reserves" resulting in secondary hypoglycemia. She also advances evidence to show that accumulation of guanidine interferes with normal glycogenolytic functions of the liver and with calcium metabolism.
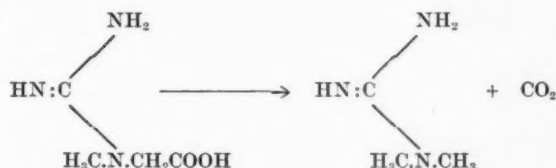
Minot and Cutler[3] report an increase in guanidine-like substance in acute experimental and clinical liver injury, and in eclampsia, all three being accompanied by the characteristic hypoglycemia. We have corroborated their findings in a small number of cases of preeclampsia as well as in hyperemesis. A normal average of presumable blood guanidine, according to Pfiffner and Myers[16] is 0.23 mg. per 100 c.c. of blood, whereas in our hyperemesis cases we found from 0.50 to 0.60 mg. and in preeclampsia from 0.65 to 1.0 mg. Minot and Cutler found values between 0.50 and 0.85 mg. in preeclampsia and eclampsia. The terms "presumable guanidine" and "guanidine-like" substances are explained in the next paragraphs.

SOURCES OF GUANIDINE AND ITS CHEMICAL IDENTIFICATION

Nothing definite is known about guanidine metabolism in the body. It is believed that one source of the guanidine grouping in the system may be the purine guanine, thus linking it with purine metabolism as an end-product. This would be consistent with the clinical view that excessive meat consumption is harmful in pregnancy toxemias, but there is not the slightest experimental evidence to establish this.

Another reasonable but unconfirmed belief of one of us (Messer) is that creatine is in some way responsible for guanidine. By reduction and demethylation creatine might form guanidine. By reduction alone methyl guanidine might be formed. Dimethyl guanidine, which we have

found experimentally to be the most toxic of these combinations, could be obtained from creatine by the mere elimination of one molecule of CO_2 as follows:

$$\begin{array}{ccccc}
& NH_2 & & NH_2 & \\
& \diagup & & \diagup & \\
HN:C & & \longrightarrow \quad HN:C & & + \quad CO_2 \\
& \diagdown & & \diagdown & \\
& H_3C.N.CH_2COOH & & H_3C.N.CH_3 &
\end{array}$$

The Tiegs-Marston reaction for the guanidines, the basis of all contemporary methods for their estimation, is not specific, developing color not only with guanidine, methyl guanidine, and dimethyl guanidine, but also with creatine, creatinine, urea, arginine, histidine, cysteine, adrenaline, and some of the alkaloids.[16] The various analytical methods include procedures attempting to separate the guanidines from the other chromogens, with varying success. It will be seen that in the absence of dependable data on the direct isolation of guanidine bodies from the blood, our evidence for their presence there is indirect.

Nevertheless the method devised by Pfiffner and Myers[16] for estimation of guanidine compounds in the blood, which was the method used by us, minimizes the colorimetric interference of these other substances. For example, creatine which may be present and could give the same reaction is condensed by the Pfiffner-Myers technic into creatinine. This eliminates its interference because the colorimetric reaction of this substance develops so much more slowly than that of guanidine that readings may be made for the latter before the other appears.

Minot and Cutler[8] used the method of Major and Weber for their estimations. This provides for a correction for interference due to creatine.

While the objection is therefore to be offered to the finding of increased guanidine-like substances in pregnancy toxemia, that estimations of blood-guanidine are not specifically accurate, the significant fact remains that the experimental administration of guanidine compounds to animals produces a train of symptoms closely resembling clinical eclampsia.

GUANIDINE ACCUMULATION AND LIVER NECROSIS

In the association of liver damage with guanidine accumulation, which factor is the cause and which is the effect has not finally been established.

Minot and Cutler believe that the increase in guanidine results from the liver injury, being formed in the process of necrosis of liver tissue, whereas Elkourie and Larson[17] state that guanidine intoxication causes liver necrosis. Others[18, 19, 20] have made similar observations but in all except one of these recorded instances the experimental animals were killed by single lethal doses of some guanidine compound, a procedure which does not imitate the slower and more gradual accumulation of toxins which must take place in preeclampsia and eclampsia. Furthermore,

it is suggested that these investigations were controlled insufficiently to be conclusive.

It seemed a simple matter to obtain evidence for or against the idea that excessive guanidine formation could precede the liver destruction, granting the obvious fact that more would form and accumulate as a direct result of this necrosis.

To discover the correct sequence of events we determined to treat normal, healthy rats with sublethal doses of guanidine until an acute or profound toxemia was produced. Some of these were to be allowed to die while others were to be killed. Histologic examinations of the liver and kidneys of all of them were to be conducted, and if pathologic changes, such as liver degeneration or necrosis, were found in properly controlled animals it should then be apparent that this was a result of the guanidine poisoning.

Extensive investigations of the biochemical and clinical effects of guanidine poisoning have been made by others and will be briefly outlined for the sake of reference.

CLINICAL AND BIOCHEMICAL EFFECTS OF GUANIDINE ADMINISTRATION AND THEIR RESEMBLANCE TO CERTAIN CHARACTERISTICS OF ECLAMPSIA

Before proceeding to a description of the technical details of our experiments and findings, it is desirable to review briefly the clinical and biochemical results of guanidine poisoning previously referred to, especially because of their resemblance to the symptoms of preeclampsia and eclampsia.

I. Disturbance in Carbohydrate Metabolism.—Minot's explanation of the occurrence of the hypoglycemia from guanidine intoxication has been outlined above. She further reports that rats so poisoned develop one of two types of abnormality of carbohydrate metabolism; either a hypoglycemia with a liver progressively depleted of its glycogen, or one without such depletion. In the latter instance she believes that guanidine accumulation interferes with normal glycogenolysis thus being an additional factor in the loss of carbohydrates through lactic acid formation and its renal spill, without compensation in these instances from the liver stores.

II. Fluctuations in Blood Sugar.—The hypoglycemia following guanidine administration described by Watanabe in 1916[10] is such a characteristic symptom that Collip[21] later considered insulin to be a guanidine derivative, while Frank, Nothmann, and Wagner[11] synthesized "synthalin" (diguanidino-decamethylene) in an effort to provide an insulin substitute for oral administration. These latter authors in 1926 demonstrated blood sugar fluctuations and concomitant convulsions after injecting guanidine into a fasting rabbit[22] similar to those noted by Titus, Dodds and Willetts[1, 2, 3, 5] in eclampsia. They also maintained the blood sugar levels and alleviated the symptoms in their toxic animals by injections of dextrose.

III. Increase in Blood Uric Acid, Amino Acids, and Lactic Acid.—Harding, Allin and Van Wyck[20] report an increase in blood uric acid following guanidine administration, while Blatherwick, Sahyun and Hill[15] found an increased amount of amino nitrogen in the blood of animals treated with synthalin. As mentioned above, Minot[15] has demonstrated an increase in blood lactic acid and its excretion in the urine, independent of muscular exertion.

IV. Increase in Blood Pressure.—Major and his coworkers have repeatedly demonstrated the pressor action of guanidine. Major[24] showed that the hypertension is brought about by vasoconstriction, and that this effect could be elicited, not only by parenteral administration, but also by absorption from the alimentary tract, and most readily from the ileum.

V. Edema.—Ellis[25] showed that the brain, kidney and striated muscle taken from animals in acute guanidine tetany had a higher water content than the same tissues from normal animals; and that the blood of rats similarly treated had an abnormally low water content.

VI. Renal Damage.—Elkourie and Larson[17] state that guanidine poisoning in animals results in a simple tubular necrosis of the kidney, in which the glomeruli are very little affected. Blatherwick, Sahyun and Hill[18] found that the administration of synthalin to rabbits caused nephritis accompanied by uremia. We, too, have certain histologic evidence or this occurrence in experimental animals.

VII. Coagulability of the Blood.—Major[26] investigated the effect of guanidine on the clotting time of the blood and found that while there seemed to be a tendency for the latter to be shortened, the variations were within normal limits, and no constant change could be shown. We plan to repeat this work.

VIII. Convulsions.—These are a most noteworthy accompaniment of guanidine intoxication. Frank, Stern and Nothmann[27] describe the characteristic differences in muscular response between cold blooded animals, the lower mammals such as the mouse and the rabbit, and higher mammals such as the cat and the dog. Using dimethyl guanidine, they were able to elicit in the cat a series of periodic convulsive seizures closely approximating those of human eclampsia. Guanidine poisoning is not always marked by convulsions but a certain number of animals (Minot's) showed merely profound depression during the intoxication. These were the animals in which Minot found the liver's glycogen stores still relatively high, but as stated before these animals received only one or two large doses of the guanidine.

In our experiments we attempted to imitate the slower progression of an eclamptic process by administering sublethal doses of guanidine over a period of time, in order to obtain a cumulative effect. Our animals generally showed a progressive lethargy, then paralysis of the hindquarters, and presently convulsions followed by death. It was relatively uncommon not to observe convulsions in the animals treated as described.

TECHNICAL DETAILS OF INVESTIGATION

The development of various technical steps in the investigation which required elucidation caused our series of experiments to arrange itself into four groups. For example, even the proper dosage of guanidine and the proper frequency of its administration was uncertain and needed to be determined. Other factors are outlined below.

DOSAGE AND TOXICITY

Group I was that in which the toxic but sublethal and finally lethal doses of guanidine and dimethyl guanidine for rats was determined.

We desired at first to develop a toxic dosage which could be prolonged over several days so as to have a progressive, cumulative effect on the organism. It is hardly to be expected that a single, fatal dose would have time to cause much if any histologic change in the liver or kidneys, although it is on such evidence as this in some instances that conclusions have been based.

Twelve rats were treated, 6 with guanidine, 4 with dimethyl guanidine, and 2 with injections of normal salt solution as controls.

Guanidine carbonate neutralized to litmus to prevent sloughs, and dimethyl guanidine sulphate were the preparations used throughout the experiments.

In the Group I experiment the dosage of each of these varied from 0.2 gm. to 0.5 gm. per kilo of body weight, this eventually being increased if necessary to do so in order to cause death. The test was not allowed to go over fifteen days.

All animals given guanidine showed convulsions before death; 2 died after the second daily dose, one after the third, and one after 9 daily doses. The largest number of injections was ten over fifteen days, increasing the dosage from 0.2 to 0.48 gm. per kilo in two animals.

When convulsions were established four animals were killed by a sudden blow, while two died in convulsions before this was done.

Dimethyl guanidine in all instances in this and the other groups has proved more toxic than guanidine.

Two animals died after the first injection of 0.5 gm. of dimethyl guanidine per kilo of body weight.

Two received 0.2 gm. for 6 injections at daily intervals.

All 4 had convulsions.

METHODS OF CONTROLLING EXPERIMENTS

The 2 controls were given 10 one c.c. doses of 0.9 per cent sodium chloride solution at the same intervals as the guanidine dosage.

The histologic findings in these controls were abnormal for control animals (see Table I), and we have not determined whether or not this could be due to the salt solution.

It was apparent from these, however, that neither conclusions nor assurance were to be had from a small series of controls. Obviously it would be necessary in judging the pathologic results of any treatment to have an ample series of experi-

TABLE I.

GROUP ONE: Rats Receiving Guanidine and Dimethyl Guanidine: Small Doses at Daily Intervals.

Number	Dates	Doses	Dosage per kilo Body Wt.	Progressive Clinical Data	Pathologic Findings
103	1-13 1-14, 32	2	Guanidine Ea. 0.5 gm	No symptoms; Dead in rigor; still warm	Liver: Diffuse cloudy swelling; pole staining midzonal areas in which cytoplasm is foamy; periportal thrombosis; central areas lobules stain well. Kidney: Cl swelling conv tubules.
105	1-13,14 15, 32	3	Guanidine Ea 0.5 gm	Motor paralysis; Spasmodic movements; Moribund, Killed	Liver: Cloudy swelling periphery of lobules; hemorrhage in isolated areas with beginning necrosis. Kidney: Marked cl swelling conv tubules, desquamation lining cells; interstitial hemorrhage; debris in tubules
108	1-13,14,15,18,20, 21,22,23,24, 32	9	Guanidine 0.3 to 0.5 gm	Convulsive movements, Paralysis, Convulsions Dead; Still warm	Liver: Diffuse cl swelling; intracellular hemorrhage periportal thrombosis; isolated areas with hemorrhage with beginning necrosis. Kidney: Similar to 105
109	1-13,14 15, 32	3	Guanidine Ea 0.5 gm	No symptoms 2 days; Convulsions, Killed	Liver: Moderate cloudy swelling; some interstitial hemorrhage Kidney: Similar to 105
112	1-13,14,15,18,20,21 22,23,24,27, 32	10	Guanidine 0.2 to 0.48 gm	No symptoms 11 days; Torpid; Paralysis, Violent convulsions Killed	Liver: General moderate cloudy swelling in parenchyma Kidney: Similar to 105
113	1-13,14,15,18,20,21 22,23,24,27, 32	10	Guanidine 0.2 to 0.48 gm	No symptoms 11 days; dyspnea, Torpid; Convulsions, Moribund, Killed	Liver: Peripheral cells normal, central cells stain poorly, mottling, indication early central change Kidney: Similar to 105
101	1-14, 32	1	Dimethyl Guanidine 0.5 gm	3 to 4 hrs after injection violent spasms, Killed	Liver: Diffuse cloudy swelling; moderate interstitial hemorrhage Kidney: Hemorrhage; cl swelling parenchyma, interstitial chr cell infiltration
102	1-14, 32	1	Dimethyl Guanidine 0.5 gm	4 hrs after injection mild convulsions; Found dead in rigor at 9 hrs, Warm	Liver: Marked periph cloudy swelling with some hemorrhage and suggestion of cell changes in hem areas. Kidney: Cl swelling conv tubules; mod hemorrhage in medulla
106	1-13,18,20,21,22, 23, 32	6	Dimethyl Guanidine 0.2 to 0.41 gm	Found dead last day; No convulsions; Warm.	Liver: Diffuse intracell hemorrhage and diffuse cloudy swelling Kidney: Cl swelling conv tubules; moderate medullary hemorrhage
107	1-13,18,20,21,22, 23, 32	6	Dimethyl Guanidine 0.2 to 0.4 gm	Convulsions last day Killed	Liver: Moderate diffuse cloudy swelling, no necrosis Kidney: Similar to 106
111	Controls 15 days	10	NaCl 0.9% 1 c.c. injection	No symptoms Killed	Liver: Intracellular hemorrhage, central; some chr. hepatitis Kidney: Resembles 105
110	15 days	10	NaCl 0.9% 1 c.c. injections	No symptoms Killed.	Liver: Normal; small areas fat infiltration peripheral; some chr. hepatitis Kidney: Resembles 105

Summary:　10 experimental animals, 2 controls. 9 of 10 showed convulsions. 2 controls apparently healthy.

Liver Changes: Cloudy swelling 9 (Peripheral 4, general 5, central 0); Hemorrhage 6 (Peripheral 2, general 4, central 0); Beginning necrosis 2; Periportal thrombosis 2 ; Changes in central cells 1

Kidney Changes: All specimens showed signs of irritative changes.

Controls:　Showed sufficient changes from normal (livers and kidneys) to make experiment merely suggestive but inconclusive Experiment establishes sublethal and lethal dosage guanidine for rats.

TABLE II

GROUP TWO: *Rats Receiving Guanidine and Dimethyl Guanidine. Toxic Doses Daily - Lethal Effect in 4 days.*

Number	Dates	Doses	Dosage per Kilo Body Wt.	Progressive Clinical Data	Pathologic Findings.
205	2-25,26, 27,28, '32.	4	Guanidine 0.3 to 0.4 gm	No symptoms until last day. Violent Convulsions; Killed	Liver: Moderate cloudy swelling; small amount hemorrhage. Kidney: Moderate cloudy swelling; moderate medullary hemorrhage
211	2-25,26, 27,28, '32.	4	Guanidine 0.32 to 0.42 gm	No symptoms until activity 3rd day 4th day tetany; died in rigor.	Liver: Diffuse cloudy swelling and hemorrhage, mostly central. Kidney: Cloudy swelling conv. tubules; moderate medullary hemorrhage.
214	2-25,28, 27,28, '32	4	Guanidine 0.3 to 0.4 gm	No symptoms until final twitching paralysis, and death.	Liver: Diffuse cloudy swelling and hemorrhage, mostly central. Kidney: Similar to 211
216	2-25,26,27, 28,29, '32	5	Guanidine 0.3 to 0.61 gm	Occasional twitching, finally paralysis; killed when moribund	Liver: Slight cloudy swelling and hemorrhage. Kidney: Moderate cloudy swelling conv. tubules and moderate medullary hemorrhage.
218	2-25,26, 27,28, '32.	4	Guanidine 0.3 to 0.4 gm	No symptoms until final weak convulsions Killed	Liver: Isolated areas peripheral fatty degeneration, begin. necrosis and hemorrhage. Kidney: Similar to 211 but less pronounced.
226	2-25, '32.	1	Guanidine 0.3 gm	Found dead, still warm and limp.	Liver: Slight cloudy swelling and little hemorrhage. Kidney: Similar to 211 but less pronounced.
230	2-25,26,27, 28,29, '32	5	Guanidine 0.3 to 0.70 gm	Activity; finally twitching. Killed.	Liver: Diffuse cl swelling and areas of hem. Peripheral cell damage with hemorrhage. Kidney: Similar to 211
243	2-25,26, 27, '32	3	Guanidine 0.29 to 0.3 gm	Convulsions and twitching; Killed.	Liver: Similar to 230. Kidney: Similar to 211
244	2-25,26, 27,28, '32	4	Guanidine 0.3 to 0.38 gm	Convulsions and twitching; Killed	Liver: Similar to 230. Kidney: Similar to 211.
245	2-25,26, 27,28, '32	4	Guanidine 0.28 to 0.4 gm	No symptoms until moribund. Killed.	Liver: Similar to 230. Kidney: Similar to 211.
209	2-25,26,27, 28,29, '32	5	Dimethyl Guanidine 0.2 to 0.57 gm	No symptoms until moribund. Killed.	Liver: Moderately diffuse fatty degeneration and cl swelling in periphery. Kidney: Cl swelling conv. tubules; mod. hemorrhage in medulla.
217	2-25,26, 27, '32	3	Dimethyl Guanidine 0.2 to 0.3 gm	Moribund; Killed.	Liver: Mod. granular change and cl swelling in peripheral cells. Kidney: Similar to 209.
223	2-25,26,27, 28,29, '32.	5	Dimethyl Guanidine 0.2 to 0.46 gm	Violent convulsions, Moribund; Killed.	Liver: Moderate fatty degeneration and cl. swelling in periphery. Kidney: Similar to 209.
231	2-25,26, 27, '32	3	Dimethyl Guanidine 0.2 to 0.3 gm	Died in rigor; autopsy while still warm.	Liver: Similar to 209. Kidney: Similar to 209.
234	2-25,26,27, 28,29, '32	5	Dimethyl Guanidine 0.2 to 0.38 gm	No symptoms until last day Apathetic. Killed	Liver: Diffuse cl. swelling and areas of hemorrhage. Slight peripheral cell damage. Kidney: Similar to 209.
237	2-25,26, 27, '32	3	Dimethyl Guanidine 0.19 to 0.3 gm	3rd day moribund but still reacting vigorously Killed	Liver: Diffuse cl swelling; hemorrhage; suggestion cellular damage. Kidney: Similar to 209.
238	2-25, '32.	1	Dimethyl Guanidine 0.2 gm	Found dead, diaphragmatic spasm; Still warm at autopsy.	Liver: Chronic hepatitis; mod congestion separating cell columns in many areas. Kidney: Cloudy swelling.
239	2-25,26,27, 28,29, '32	5	Dimethyl Guanidine 0.2 to 0.48 gm	Violent convulsions; Gasping; Jumping; Moribund; Killed.	Liver: Diffuse peripheral fatty degeneration and periph cl. swelling Kidney: Similar to 209.
240	2-25,26, 27, '32	3	Dimethyl Guanidine 0.2 to 0.3 gm	3rd day sick, limp; Found dead; Still warm.	Liver: Diffuse cl swelling; hemorrhage; suggestion cellular damage. Kidney: Similar to 209.
246	2-25,26,27, 28,29, '32	5	Dimethyl Guanidine 0.2 to 0.45 gm	Violent convulsions; Coughing; Killed.	Liver: Diffuse peripheral fatty infiltration. Few normal liver cells. Kidney: Similar to 209.
Controls No. 204 225 208 227 210 228 213 229 222 247 224		5	Physiologic Salt Solution 1 c.c. daily hypo. injection	No symptoms.	Liver: All showed a certain amount of cloudy swelling; otherwise normal except 225 which showed, in addition, moderate central fatty infiltration. Kidneys: All showed slight cloudy swelling and medullary hemorrhage except 213 which showed no hemorrhage. 227 showed in addition, interstitial cell infiltration (chronic).
Controls No. 206 232 207 233 212 235 215 236 219 241 220 242 221	5 days 2-24 to 28, 32.	0	No medication for these controls merely kept on same diet as others and killed	No symptoms.	Liver: All normal except for slight cloudy swelling. Kidneys: 232, 233, and 235 showed slight cloudy swelling; 241 moderate cloudy swelling and medullary hemorrhage; 236,242,206,207,212,215,219,220, and 221 were normal. 232,233,235, and 241 findings much less marked than in guanidine and dimethyl guanidine series.

Summary: (a) 20 experimental animals; (b) 11 salt solution controls and (c) 13 negative controls.

    (a) 11 were seen having convulsions; 2 were questionable, and 7 were not seen to have convulsions.
    The size of the group made careful clinical observations difficult.
    (b) and (c) All controls were apparently healthy.

Liver changes: Cloudy swelling 13 (Peripheral 6, general 5, central 2); Hemorrhage 12 (Peripheral 6, general 4, central 2);
    Beginning necrosis or cell damage 8 (Periph. 5, gen'l 3); Fatty degen. 6 (Periph. 5, gen'l 1); Chr. hepatitis 1.

Kidney Changes: Cloudy swelling 20; Hemorrhage 19.

Controls: Liver condition described as "slight cloudy swelling" is general; all fields show uniformity; one specimen showed
    central fatty infiltration. Liver conditions described in experimental animals therefore represents deviation from normal.
    Kidneys show practically same changes, but to a lesser degree, seen in experimental animals.

Experiment shows that guanidine compounds, in toxic doses, cause suggestive, but not specific or uniform histologic changes in liver and
    to a lesser degree in kidneys. From this study it was decided to abolish the 24 hour interval during which tissue regeneration
    could occur   —   see Table III.

mental animals with a similarly large series of control animals supposedly normal. In this way the general incidence of occurrence of histologic change in treated animals could be compared with that in the general run of supposedly normal animals.

Moreover, with large numbers the control series could be divided between those receiving physiologic salt solution injections, and those merely kept under the same general conditions as all, and killed about when the tested animals died. To give one group of control rats an injection of fluid comparable to the bulk of the guanidine injection determines the validity of the possible objection that this mechanical process causes infarcts and thrombosis. All animals were kept on a liberal diet, which included cracked corn in unlimited quantity.

LARGER DAILY DOSAGE OVER SHORTER INTERVAL

Group II experiment was conducted in practically the same way, that is, daily injections but the dosage was so planned as to cause death in four days.

This group was composed of 10 rats treated with daily doses of guanidine, 10 with dimethyl guanidine, 11 with physiologic salt solution, and 13 negative controls killed by a blow.

ELIMINATION OF LIVER REGENERATION POSSIBILITIES

Because the histologic examination of the tissues of the foregoing animals showed findings which were still suggestive but not conclusive a suggestion made by Dr. A. J. Bruecken was adopted. This was that the life cycle of the rat is so short as compared to that of a human being that an interval of twenty-four hours between injections allows too great an opportunity for regeneration of liver cells between doses as compared to the presumably constant formation of toxins in a preeclamptic woman.

TABLE III

Group Three: Rats Receiving Guanidine: Lethal Dose Divided Into Eight (8) Hourly Intervals - Lethal Effect in One Day.

Number	Date	Doses		Progressive Clinical Data	Pathologic Findings
401	3-28-'32	4	Guanidine 0.126 gm	1 No symptoms 2 Lethargic; Spasmophic 3 Convulsive movements 4 Convulsion, Killed	Liver: Scattered large vacuoles (fatty infiltration); general hemorrhagic congestion mostly around central veins. Cells stain well Kidneys: Moderate cloudy swelling convoluted tubules.
402	3-29-'32	8	Guanidine .0.07 gm	1&2 Quiet 3-4 Slight spasms 5 Slight convulsions 6-7 Eating 8 Convulsions. Died	Liver: Hemorrhagic congestion, mostly central, displacing in some areas liver columns around central veins. Kidneys: Moderate cloudy swelling convoluted tubules.
403	3-30-'32	5	Guanidine 0.07 to .068 gm	2 Slight convulsions. 3 No symptoms 4 Spasmophilia 5 Paralyzed twitching died	Liver: Congestion and areas of hemorrhage with cells swollen and columns partly disintegrated with granular cytoplasm; few areas central and peripheral resembling focal necrosis. Kidneys: Cloudy swelling convoluted tubules.
404	3-31-'32	8	Guanidine 0.063 gm	No symptoms until after 8th dose; paralysis, spasmophilia; Killed	Liver: Moderate congestion; generalized cloudy swelling cells with moderate breakage of columns. Kidneys: Moderate cloudy swelling convoluted tubules.
405	3-31-'32	8	Guanidine 0.062 gm	No symptoms until after 8th dose; paralysis, spasmophilia; Killed	Liver: Occasional oval vacuole (fatty infiltration) Moderate central congestion; section stains uniformly. Kidneys: Moderate cloudy swelling convoluted tubules.
406	3-31-'32	8	Guanidine 0.060 gm	No symptoms until after 8th dose; paralysis, spasmophilia; Killed	Liver: Moderate congestion especially around central vein. Scattered single cells with fatty degeneration and infiltration Kidneys: Slight cloudy swelling convoluted tubules.
Controls 407 410 408 411 409 412	3-31-'32	O	No medication	Normal animals killed by stunning blow, and bleeding.	Livers: No cellular change; poor histologic sections (technical). Kidneys: Slight cloudy swelling convoluted tubules; less than changes noted in experimental animals.

Summary: 6 experimental animals, 6 controls. 3 of 6 had convulsions; all were spastic.
Liver Changes: Cloudy swelling, general 1; Hemorrhage 6 (General 2, central 4); Fatty infiltration or degeneration 3 (General 2, central 1); Necrosis 1.
Kidneys: Cloudy swelling conv. tubules 6.
Controls: Livers negative; Kidneys show moderate cloudy swelling.
Experiment developed more suggestive evidence of liver damage in fatty changes within and between cells.

Consequently in Group III 12 rats were utilized. Six were given hourly injections of guanidine, each dose being one-eighth of the lethal dose. Six untreated controls were examined.

UTILIZATION OF ANIMALS WITH PLACENTATION SIMILAR TO HUMAN BEINGS

In Group IV guinea pigs were utilized because their placentation resembles that of the human being. We have been impressed with the fact that the work of Dieckmann[28, 29] is the only one which seems to have approached by experimental formation the lesions thought of by many to be typical of eclampsia; namely the focal necrosis in the periphery of the liver lobules.
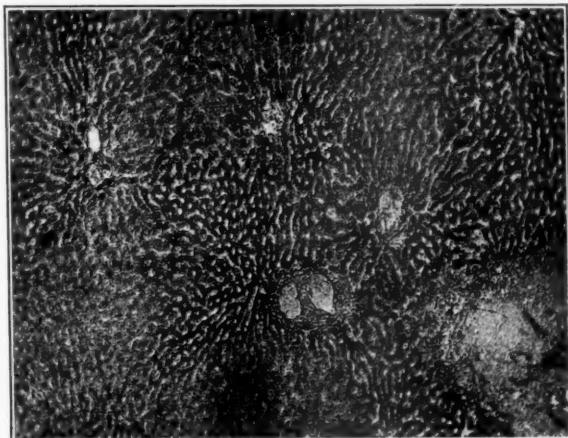

Fig. 1.—Liver from Rat No. 103; guanidine injections (Table I). Shows mottling due to differences in staining qualities of cells in various areas; beginning thrombosis in portal vein branch.
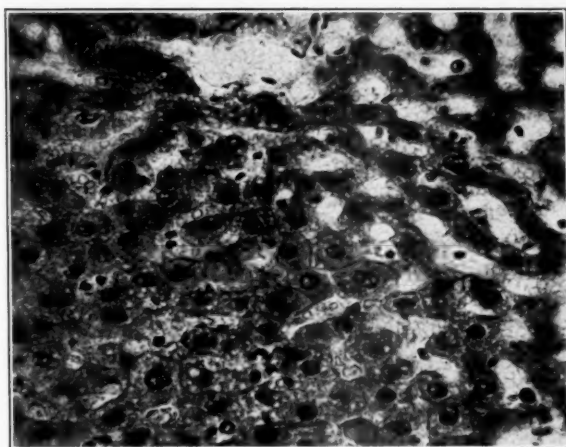

Fig. 2.—Same as Fig. 1; high power. Shows congestion, swelling and "foamy" cytoplasm, also breaking-up of liver cell columns in certain areas.

Dieckmann's suggestion that syncytial tissue and chorionic villi may be a source of tissue fibrinogen exciting this lesion is a reasonable one, and we plan in our next work to determine whether or not the combination of dimethyl guanidine injections into animals that are pregnant, will go any further toward completing the chain of evidence being investigated. The question of the mechanical effect of these injections arises although even complete obstruction of the portal vein does not cause necrosis of liver tissue. Closure of branches of the portal vein as in thrombosis may

result in hemorrhagic infarcts, which latter while being "death" of tissue do not present the same picture as focal necrosis.

We found in Group IV that guinea pigs were more resistant to the dimethyl guanidine injections than rats had been.

Four guinea pigs were used for the experiment and 2 were killed as controls. These animals required 12 injections daily over four days, and of course the element of regeneration during the night intervals must be considered.
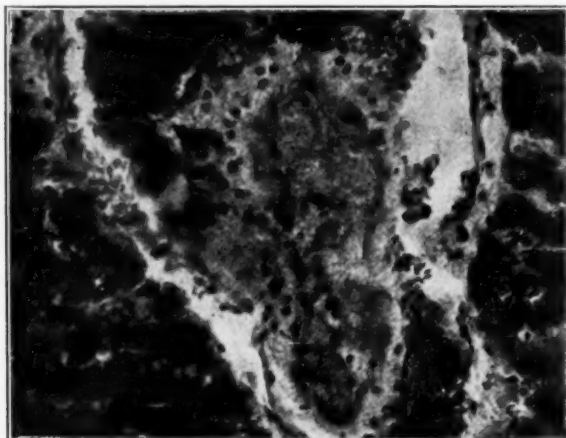

Fig. 3.—Liver from Rat No. 108 (Table I) ; high power, showing thrombosis branch of portal vein.
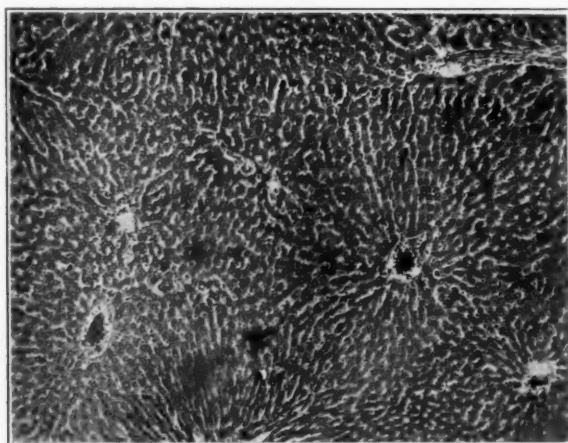

Fig. 4.—Liver from Rat No. 113 (Table I) ; shows congestion around central vein, beginning breaking-up of liver cell columns.

The Group IV experiment resolved itself essentially into an investigation to determine the toxic and lethal dosage of dimethyl guanidine for guinea pigs when given at hourly intervals, thus being somewhat similar to that of Group III for rats.

This links up so closely with the projected work just discussed that it seems advisable to say for the present, merely that the organs of these animals showed degenerative changes similar to those outlined in the three tables. This can be discussed more in detail in connection with the investigation now under way, which is mentioned now merely as a preliminary report.
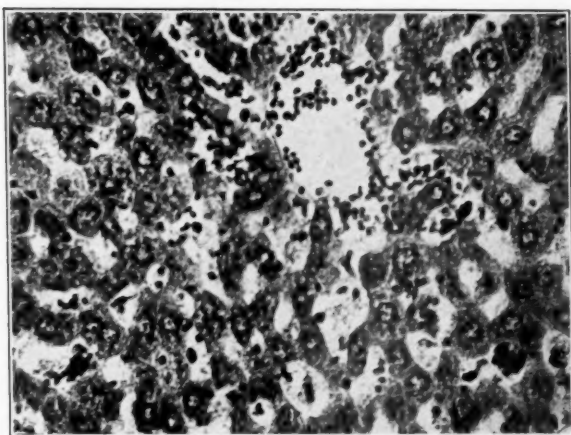
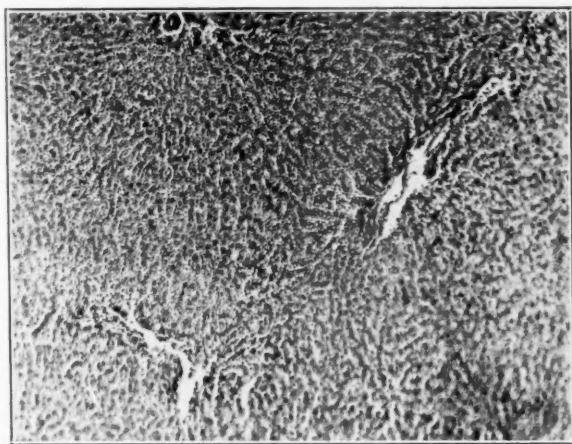Fig. 5.—Same as Fig. 4; high power, cloudy swelling and congestion noticeable.

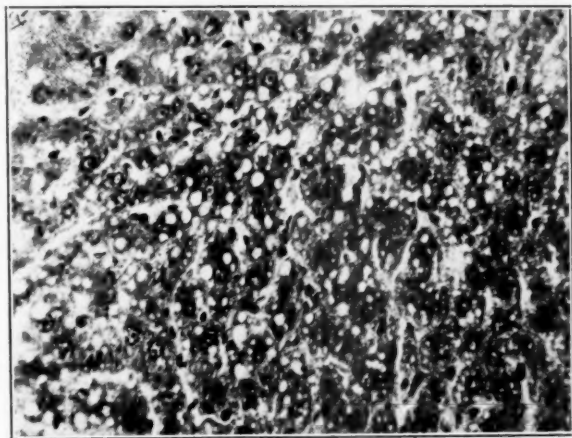Fig. 6.—Liver from Rat No. 209 (Table II). Marked fatty degeneration in periphery of lobules.

Fig. 7.—Same as Fig. 6; high power. Beginning necrosis also noticeable.

DISCUSSION OF HISTOPATHOLOGIC RESULTS

The foregoing details have been summarized in order to eliminate them from and thus condense the tables.

The results are shown in detail in Tables I to III and in Figs. 1 to 14.
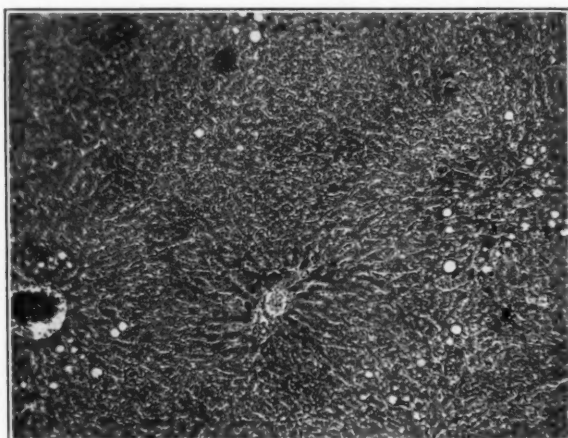
Fig. 8.—Liver from Rat No. 246 (Table II). Peripheral fatty degeneration ("infiltration") and beginning necrosis.
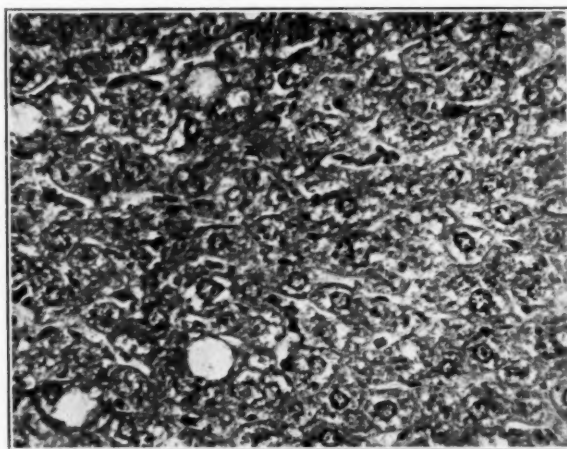
Fig. 9.—Same as Fig. 8; high power. Shows swelling, granular and fatty changes in cytoplasm with loss of cell outline.

The recent important clinicopathologic study of eclampsia by Acosta-Sison[30] who performed complete autopsies on 38 patients has raised anew the question as to the specificity of any liver lesions in eclampsia. It is true that many authorities, notably Williams,[31] have regarded peripheral necrosis in the lobule as the characteristic liver lesion in eclampsia. In summarizing these 38 autopsies, Acosta-Sison says "focal areas of hemorrhagic necrosis and fatty degeneration predominantly in the periphery of the liver lobule were observed only in a few cases (4 cases), the liver lesions were rather scattered indistinctly (this may be a misprint for

indiscriminately) in the lobule with special susceptibility for the central areas.''
Acosta-Sison finds that hemorrhagic, fatty, and degenerative changes may affect
the eclamptic liver alone or in combination.

Fatty degeneration, according to Beattie and Dickson[22] may be regarded as a
retrogressive change associated with the appearance of fatty granules or globules in
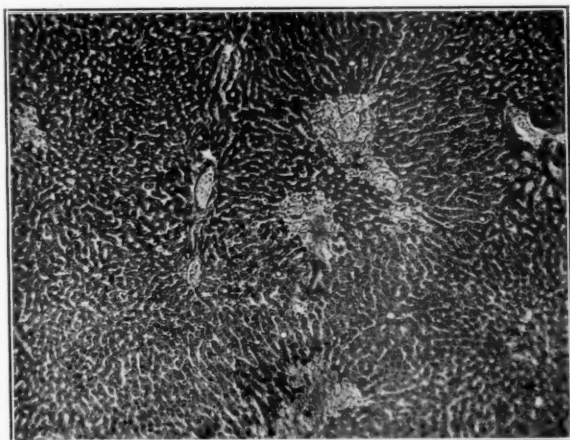
Fig. 10.—Liver from Rat No. 403 (Table III).   Focal necrosis, both central and
peripheral.
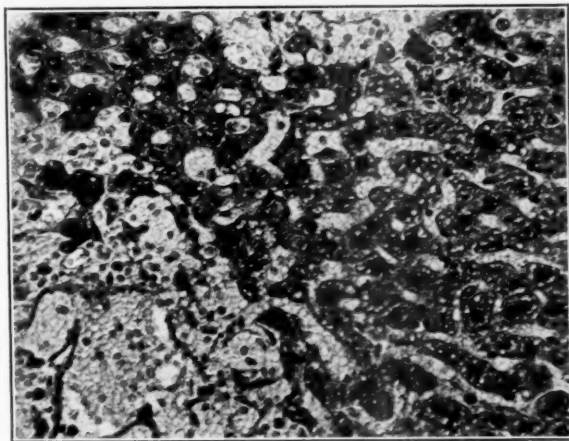
Fig. 11.—Same as Fig. 10; high power.   Shows edges of areas of focal necrosis, hemor-
rhage, granular cytoplasm.

the cytoplasm of the cell, this being one of the common methods of decay in the
animal cell.   It frequently occurs as a sequel to, or in combination with cloudy
swelling.   Fatty infiltration and other degenerative conditions are frequently found
associated with fatty degeneration.   They quote authorities who state that the term
''fatty degeneration'' conveys a wrong impression and should be termed ''degenera-
tive fatty infiltration'' as being an encroachment of fat from the outside deposited
within cells whose vitality is lowered so that they cannot use it up.

The foregoing is a prelude to the statement of the impression which we have gained from these series of animals which were given toxic doses of guanidine or dimethyl guanidine. Suggestive changes in their livers have developed, such as cloudy swelling, interstitial hemorrhage, beginning periportal thrombosis, and fatty infiltration and degeneration both
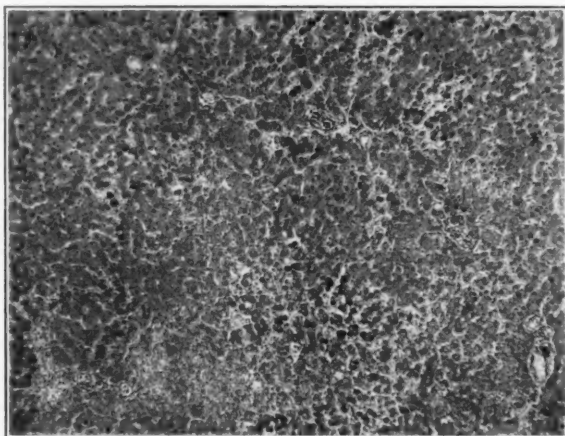
Fig. 12.—Human eclamptic liver (low power). Shows cloudy swelling, hemorrhage, and focal necroses both central and peripheral.
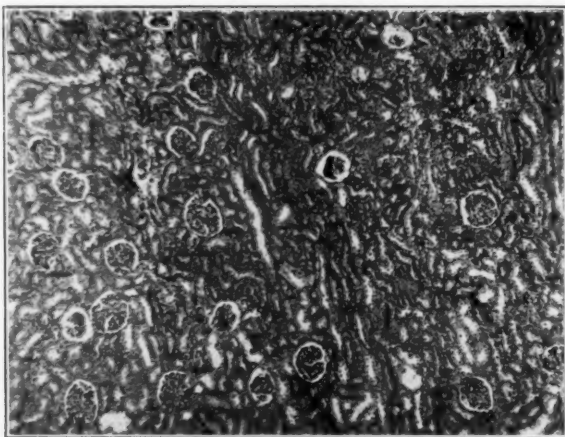
Fig. 13.—Kidney from Rat No. 238 (Table II). Shows cloudy swelling of convoluted tubules; desquamation lining cells; debris in tubules.

peripheral and central, as well as differences in the staining qualities of the cells in various areas of the liver lobules. All of these are illustrated in Figs. 1 to 14, and the ones showing peripheral and central focal necrosis are especially interesting in view of the opinions held by some on this subject.

We are not satisfied that these histologic alterations represent anything more than early degenerative changes, similar perhaps to those

found in about 29 per cent of Acosta-Sison's eclamptics, and we do not feel that true focal necroses were produced in any more than one of these animals despite the suggestive appearance of some of the photomicrographs. At the same time we are still unconvinced that this latter is an invariable and characteristic feature of eclampsia.

The histologic changes noted in the kidneys were thought to be strikingly typical of toxic irritation until those of the control animals were examined. In practically all of those to which the guanidine substances were given, it was noted that cloudy swelling of the convoluted tubules, with desquamation of the lining cells, debris in the tubules, and interstitial hemorrhage occurred. That this did not represent as profound a change as at first thought, was demonstrated by the finding that this was also the case to a lesser degree in many of the control
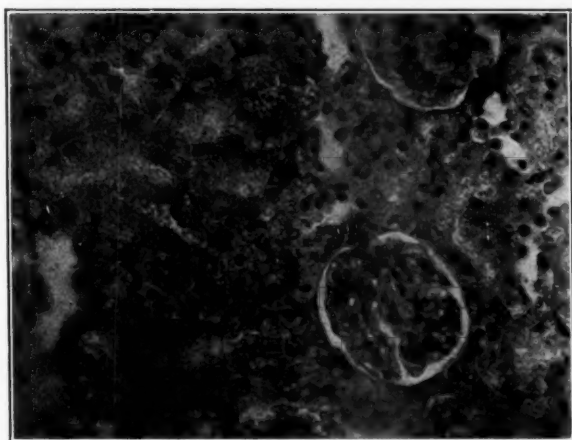
Fig. 14.—Kidney from Rat No. 403; high power.   Marked cloudy swelling and desquamation.

animals. It was usually possible to distinguish between a control and an experimental animal's renal tissue and to say that the control more nearly represented normal, but cloudy swelling of some degree occasionally accompanied by medullary hemorrhage were almost constant occurrences in the kidneys of apparently healthy control animals.

It is suggestive and of interest that there is a metabolic toxin which can so accurately reproduce in animals the major clinical symptoms of eclampsia, and likewise develop some of the histopathologic changes seen in this disease. This experiment was conducted on nonpregnant animals and the positive results which have been obtained in the form of degenerative histologic changes in the liver and kidneys seem to be sufficiently convincing to warrant carrying the experiment further.

The next step as stated above is to duplicate the details of the Group IV experiment in animals advanced in pregnancy and having the same type of placentation as human beings.

SUMMARY

1. Several investigators have now demonstrated various biochemical or metabolic disturbances in eclampsia, such as fluctuations in blood sugar during the attack, and a trend toward hypoglycemic levels. Increase in blood uric acid and lactic acid, increase in blood pressure, edema, albuminuria, and convulsions are commonplace symptoms.

2. Reports have been made of an increase in guanidine-like substances in the blood during preeclampsia and eclampsia.

3. By experimental administration of guanidine compounds to animals all of the foregoing clinical symptoms of eclampsia may be reproduced, including the fluctuations in blood sugar and typical convulsive seizures.

Moreover, the clinical use of certain guanidine compounds in reducing blood sugar levels in diabetics, as a substitute for insulin, has now been abandoned because of its toxic effects and its tendency to cause sudden and profound hypoglycemia.

4. Authorities have differed as to whether the increased apparent guanidinemia in instances of acute liver injury, either clinical or experimental, precedes and causes the liver tissue degeneration, or follows it having resulted from this tissue destruction.

5. The experimental injection of a single dose or two of a guanidine compound sufficient to kill an animal quickly should not be expected by an investigator to produce much if any histologic changes in the tissues of liver and kidneys, because of the abruptness of its action.

6. This experimental investigation was undertaken to determine whether or not a more or less protracted series of guanidine and dimethyl guanidine injections would, by their cumulative action, cause histopathologic changes in the liver and kidneys.

7. Degenerative changes of varying types but chiefly suggestive of early stages of hepatic degeneration have been produced in a large, controlled series of animals. These changes include cloudy swelling, interstitial hemorrhage, beginning periportal thrombosis, and fatty degeneration and infiltration both peripheral and central, as well as focal necroses similarly distributed. The kidneys showed cloudy swelling of the convoluted tubules, desquamation of lining cells, and hemorrhage.

8. These hepatic changes were less distinctive in the animals to which guanidine injections were given by single daily doses than in those receiving the injections at hourly intervals to the point of death in one day. In the former, liver cell regeneration probably takes place during the resting period. It was, for example, by the latter method that the 6 animals (Group III) were treated, of which one showed the focal necroses in the liver referred to in the preceding paragraph.

9. It is of interest that experimental administration of a metabolic toxin which can be elaborated within the body can reproduce in animals

the major clinical symptoms and at least the early stages of the histopathologic changes seen in eclampsia.

10. The exact source of an accumulation of guanidine-like substances within the body is still uncertain, and their relation to eclampsia is entirely problematic.

11. Tables detailing the pathologic findings in this series of experiments are given, and numerous photomicrographs of liver and kidneys are shown.

REFERENCES

(1) *Titus, Paul, Dodds, Paul, and Willetts, E. W.:* AM. J. OBST. & GYNEC. **14**: 89, 1927. (2) *Idem:* AM. J. OBST. & GYNEC. **15**: 303, 1928. (3) *Titus, Paul, and Willetts, E. W.:* AM. J. OBST. & GYNEC. **18**: 27, 1929. (4) *Lightbody, H. D.:* AM. J. OBST. & GYNEC. **18**: 36, 1929. (5) *Titus, Paul, Willetts, E. W., and Lightbody, H. D.:* AM. J. OBST. & GYNEC. **19**: 16, 1930. (6) *Laferty, J. M.:* AM. J. OBST. & GYNEC. **22**: 637, 1931. (7) Personal communication, Siegel, I. A., and Wiley, H. B., Univ. of Maryland, Baltimore. (8) *Minot, A. S., and Cutler, J. T.:* Proc. Soc. Exper. Biol. & Med. **26**: 607, 1929. (9) *Minot, A. S., and Cutler, J. T.:* Proc. Soc. Exper. Biol. & Med. **26**: 138, 1928. (10) *Watanabe, C. K.:* J. Biol. Chem. **33**: 253, 1918. (11) *Frank, E., Nothmann, M., and Wagner, A.:* Klin. Wchnschr. **5**: 2100, 1926. (12) *Staub, H.:* Ztschr. f. Klin. Med. **107**: 607, 1928. (13) *Staub, H., and Kung, O.:* Klin. Wchnschr. **7**: 1365, 1928. (14) *Staub, H., and Jezler, A.:* Ztschr. f. Klin. Med. **112**: 1, 1929-30. (15) *Minot, A. S.:* J. Pharmacol. & Exper. Therap. **43**: 295, 1931. (16) *Pfiffner, J. J., and Myers, V. C.:* J. Biol. Chem. **87**: 345, 1930. (17) *Elkourie, L. A., and Larson, E.:* Am. J. Physiol. **87**: 124, 1928. (18) *Batherwick, N. R., Sahyun, M., and Hill, E.:* J. Biol. Chem. **75**: 671 1927. (19) *Simola, P. E.:* Ztschr. Physiol. Chem. **168**: 274, 1927. (20) *Bodo, R., and Marks, H. P.:* J. Physiol. **65**: 83, 1928. (21) *Collip, J. B.:* Jr. Biol. Chem. **57**: 65, 1923. (22) *Frank, E., Nothmann, M., and Wagner, A.:* Arch. f. exper. Path. u. Pharmacol. **115**: 55, 1926. (23) *Harding, V. J., Allin, K. D., and Van Wyck, H. B.:* J. Obst. & Gynec. Brit. Emp. **31**: 1, 595, 1924. (24) *Major, R. H.:* Bull. Johns Hopkins Hosp. **39**: 215, 1926. (25) *Ellis, M. M.:* Biochem. J. **22**: 937, 1928. (26) *Major, R. H.:* Bull. Johns Hopkins Hosp. **39**: 222, 1926. (27) *Frank, E., Stern, R., and Nothmann, M.:* Ztschr. f. d. ges. exp. Med. **24**: 341, 1921. (28) *Dieckmann, W. J.:* AM. J. OBST. & GYNEC. **17**: 454, 1929. (29) *Idem:* AM. J. OBST. & GYNEC. **18**: 757, 1929. (30) *Acosta-Sison, H.:* AM. J. OBST. & GYNEC. **22**: 35, 1931. (31) *Williams, J. W.:* Obstetrics, ed. 6, 1930, New York, D. Appleton & Co., pp. 654-656. (32) *Beattie, J. M., and Dickson, W. E. C.:* Pathology, General and Special, ed. 2, St. Louis, 1925, The C. V. Mosby Co., pp. 35-38.

1015 HIGHLAND BUILDING.

RECONSTRUCTION OF THE OVIDUCTS: AN IMPROVED TECHNIC WITH REPORT OF CASES*

FREDERICK C. HOLDEN, M.D., F.A.C.S., AND FRANCIS W. SOVAK, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Department of Gynecology, University and Bellevue Medical College)

WITH the increased interest in the study and the revision in the treatment of sterility, plastic surgery upon the oviducts has rapidly advanced and has found a definite place in gynecologic surgery. New and improved procedures have been frequently reported, and the end-results have shown marked advancement. However, the majority of the authors of these papers judge their results by the number of pregnancies following such procedures.

The proper evaluation of any plastic operation upon the oviducts, in our opinion, does not necessarily rest upon the percentage of cases of pregnancy following, but upon the percentage of patent oviducts after operation.

Bilaterally occluded oviducts classify sterility as absolute, and, as Meaker aptly states, "the initiation of the reproductive process is, at any rate for the time being, flatly impossible." With the oviducts remaining patent after operation, the problem becomes one of relative sterility, and the initiation of the reproductive process not definitely impossible.

This study was not primarily instituted as a problem in sterility, but with the idea of developing a new technic, or improving upon the old, in operations upon occluded oviducts to maintain patency.

Although the number of cases herein reported is small, the technic has been so developed that the procedure is now being presented for your consideration and trial. Thus a larger number of cases may be reported in the future, and a more extensive evaluation placed upon the operation and its end-results. The cases studied were selected from those ward patients who, after proper tests, were found to have bilateral tubal occlusions, while also requiring other corrective pelvic operations for retroverted uteri, prolapsed adnexal masses and ovarian cysts. Thus this study was not made as a purely experimental one at the inconvenience of the patient. No special consideration was given to age or marital status.

CLASSIFICATION OF TUBAL OCCLUSIONS

For the purpose of this study, tubal occlusions have been classified as follows:

1. Outer third, which includes those occurring in the ampullary portion, and those resulting in occlusion at the fimbriated extremity (Fig. 4).
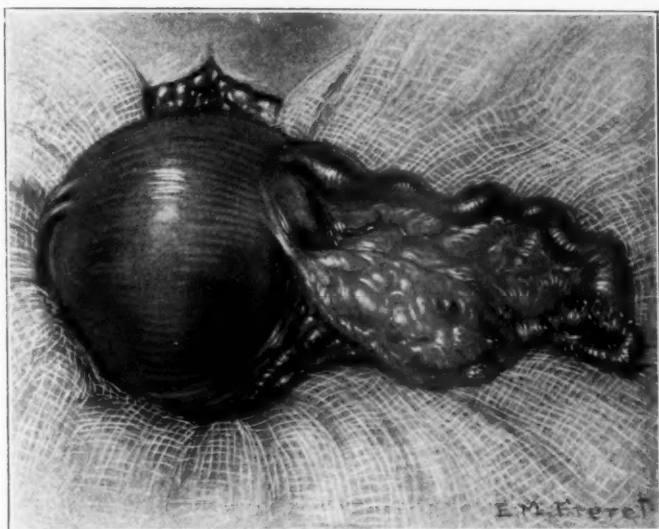
Fig. 1.—Salpingitis isthmica nodosa.   Inner two-thirds occlusion.
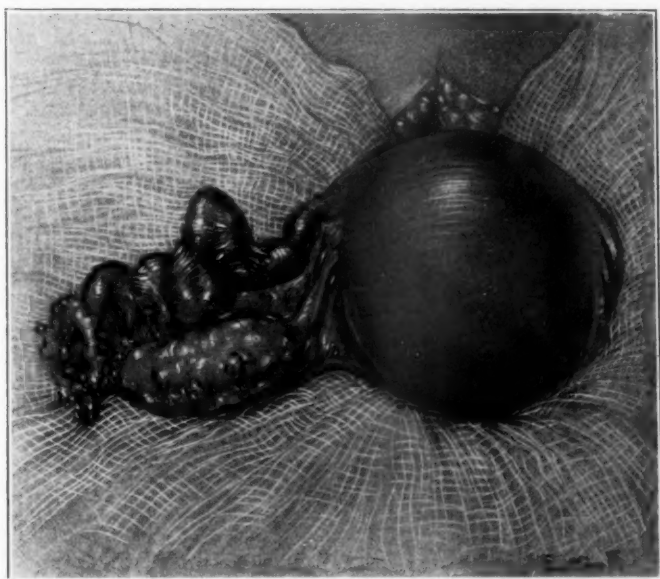
Fig. 2.—Occlusions due to kinks caused by adhesions.

2. Occlusions occurring in the inner two-thirds of the tube anywhere in the isthmic or interstitial portions (Fig. 1).

Extratubal conditions leading to occlusions, such as kinks, adhesions, or pressure by tumors, were not considered (Figs. 2 and 3).

This classification was made due to the fact that two distinct operative procedures are indicated depending upon the site of occlusion.

SELECTION OF PATIENTS

It is obvious that this operation is intended for the correction of absolute sterility, and therefore the patients selected for this procedure should be in the childbearing age, free from any developmental stigmata, and the husband proved fertile. Cases exhibiting acute or subacute pelvic pathology or tuberculous salpingitis are not suited to this procedure.
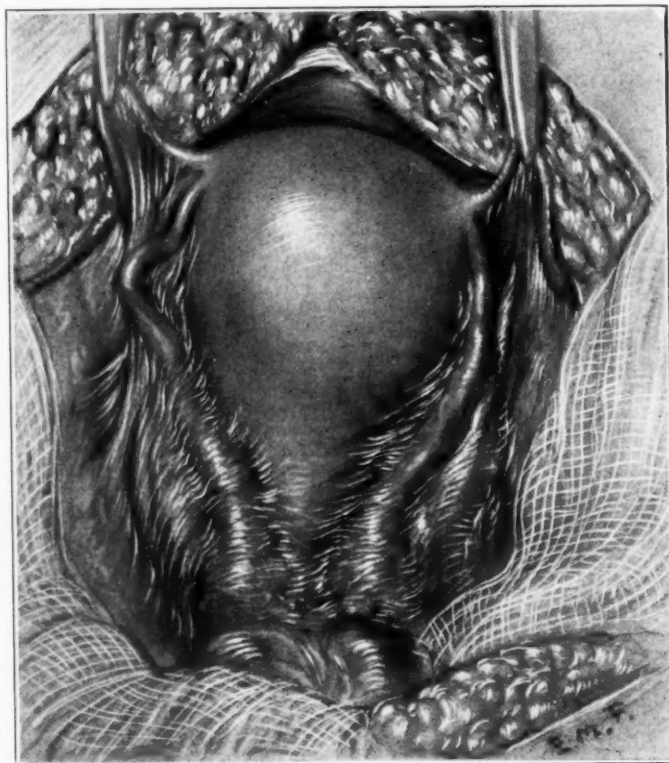
Fig. 3.—Occlusions caused by adhesions with prolapsed adnexa.

Patients with chronic adnexal disease are not acceptable until they have been under observation for at least three menstrual periods and the leucocytic count, temperature and sedimentation time show no variation from normal after bimanual examination. Patients operated upon for pathologic conditions other than sterility are at times well suited for this procedure.

PREOPERATIVE PREPARATION

Proper attention to detail in the preoperative preparation makes for the success of the end-results.

All local foci of infection in the cervix, Skene's ducts, and Bartholin's glands must be eliminated, and a Rubin insufflation test performed.

In order to assist in the recovery of the diseased tissues by a process of resolution or regeneration, the patient receives a series of treatments consisting of the application of heat per vaginam. At Bellevue we have adopted the Elliott method for this purpose. Holden and Gurnee have reported the results of this treatment in all types of pelvic infection, and it was found at the time of operation, in those cases requiring subsequent celiotomy, that inflammatory adhesions had either been absorbed or become filamentary, the previously diseased tissues appeared to be firm instead of friable, and the edema so often seen at time of operation was absent.

The number of treatments given in this series of cases varied from a minimum of 12 to a maximum of 28. The treatment was given daily for
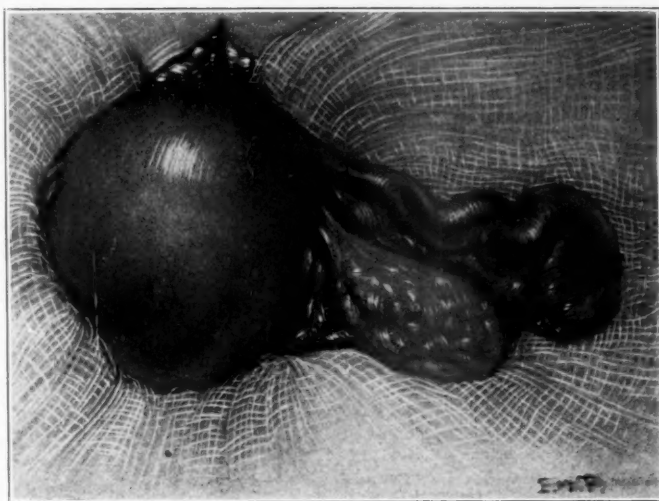
Fig. 4.—Occlusions occurring in outer third of tube, so-called clubbed tube.

a period of forty-five minutes at 128° F., at least three to four weeks before operation.

The criteria in determining the number of treatments to be given any individual are: diminution in the size of adnexal masses, or the inability to palpate adnexa previously palpable.

As these treatments at times may, by the absorption of the proliferative inflammatory process, lead to reestablishment of the patency of the tubes, the insufflation test should be repeated. The most suitable time for the operation is during the intermenstrual period.

A hysterosalpingogram was obtained pre- and postoperatively in a few of the cases for corroboration of the findings of the insufflation test.

OPERATIVE TECHNIC

Following the classification previously mentioned, oviducts having occlusions in the outer third are reconstructed by performing what we

have termed a "circumcision" operation as suggested by Bonney, everting the tube by bringing back the mucosa to the serosa for a distance of 1.5 cm. to 2.5 cm., thereby eliminating raw surfaces at the newly constructed ostium and avoiding adhesions and occlusions which are so prone to follow plastic operations.
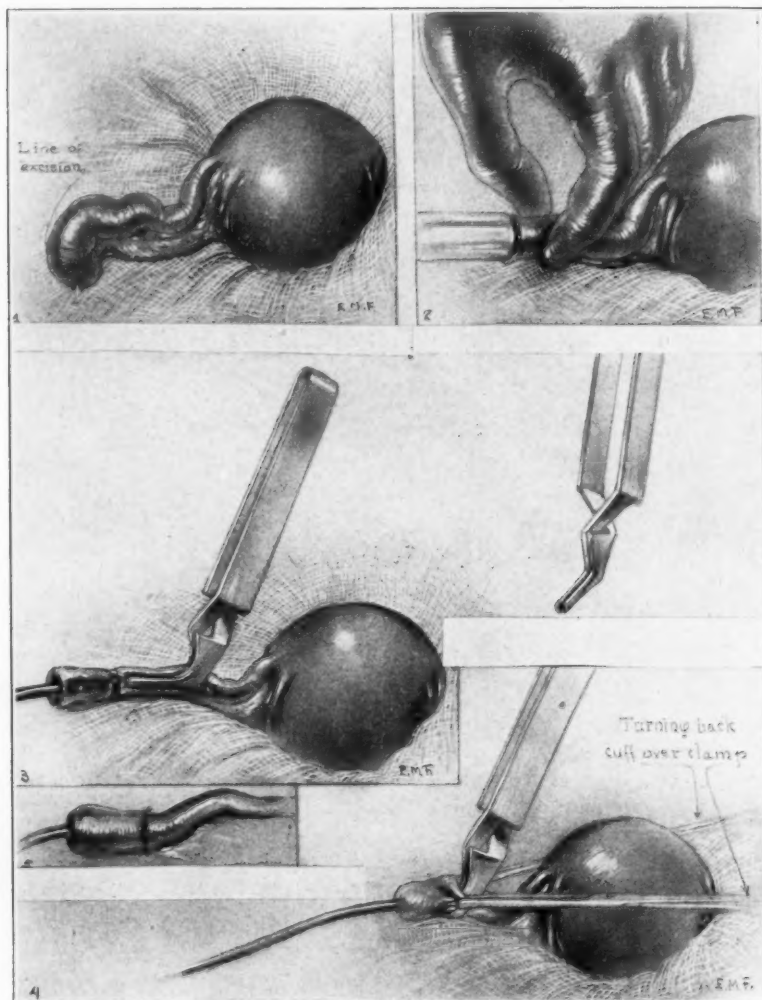
Fig. 5.—"Circumcision" operation for reconstruction of occlusions occurring in outer third of tube. 1, Line of amputation proximal to site of occlusion. 2, Testing patency of remaining portion of tube. 3, Insertion of silk bougie and application of Bonney clamp 1½ to 2½ cm. from amputated end. Circular incision down through muscularis. 4, Turning back cuff over clamp everting tube. Mucosal cuff being brought back to serosa. 5, Cuff anchored to serosa. Reconstruction complete.

Oviducts showing occlusions anywhere in the inner two-thirds are not suitable for the circumcision procedure, but are suitable for the implantation operation to be described shortly.

This implantation procedure attempts to maintain the normal anatomic and physiologic relationship of the tube to the uterus.

1. *"Circumcision" Technic.*—The tubes are handled without instruments in order to avoid trauma. The fimbriae, if occluded, are freed by blunt dissection, or if the tube be clubbed an amputation is performed proximal to the site of occlusion (Fig. 5, 1). Bleeding is controlled by the use of mosquito clamps and No. 00 plain liga-
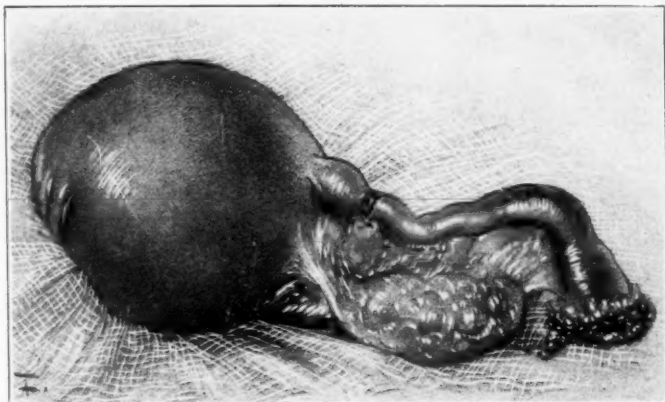
Fig. 6.—Amputation of tube proximal to site of occlusion. Site determined by use of intrapelvic insufflation syringe.
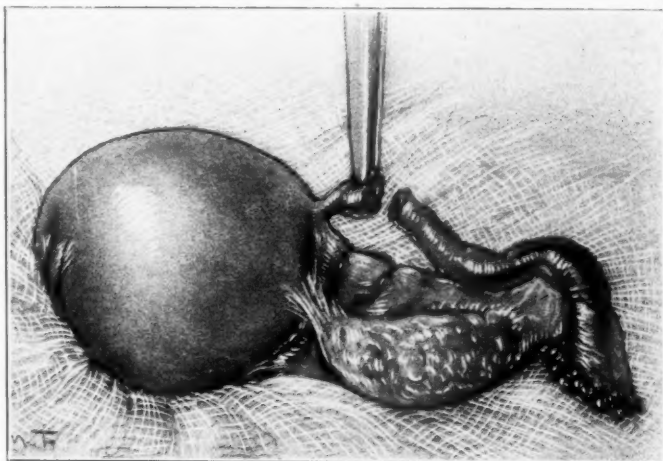
Fig. 7.—Freeing uterine portion of occluded tube from its attachment to the broad ligament. Also freeing patent portion of tube from broad ligament for a distance of one-half cm.

tures. The remaining portion of the tube is then tested for patency by air insufflation with the use of the glass syringe as suggested by Curtis (Fig. 5, 2). If patent, the air entering the uterine cavity produces a gurgling sound, and if the fundus be held, a vibratory impulse is transmitted to the fingers. If the tube be occluded at any other site it becomes dilated by the insufflated air proximal to the occlusion, and the gurgling and vibration are not present. If the remaining portion of the tube is found patent, a straight silk catheter, size No. 9 to 12 French, is inserted into the

outer third of the tube. A Bonney clamp is then placed over the tube and its inserted catheter, 1.5 cm. to 2.5 cm. from the amputated end. A circular incision is made at the distal end of the clamp down through the muscularis (Fig. 5, 3). Two fine Allis clamps are then applied to the amputated end of the tube, gently pulling it backward while the Bonney clamp is slowly pushed forward; thus the mucosa is everted and brought back to the serosa (Fig. 5, 4). This tubal cuff is held in place
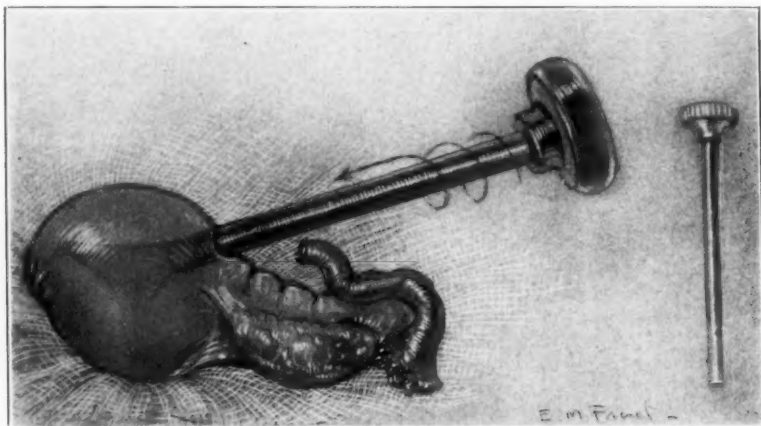
Fig. 8.—Reaming instrument applied over occluded stump of tube. With a circular movement of the instrument stump of the tube and its intramural portion is reamed out.
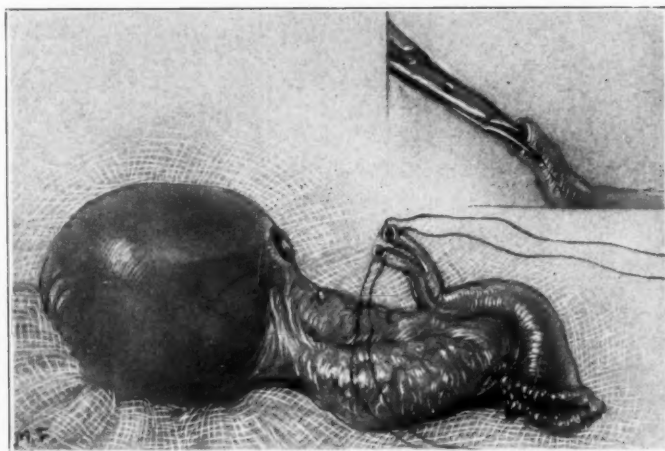
Fig. 9.—New opening into uterus following removal of occluded tube and its intramural portion. Patent portion of tube bisected longitudinally by cuticle scissors. Long No. 00 chromic sutures applied to superior and inferior ends of bisected tube.

by three interrupted No. 00 plain sutures placed so that they are concealed beneath the end of the cuff. The Bonney clamp is then gently released and removed with the catheter (Fig. 5, 5). The patency of the reconstructed tube is again tested by air insufflation with the use of the glass syringe (Fig. 5, 2). Following this the tube and ovary are suspended from the side wall of the pelvis by taking a small bite through the pelvic peritoneum and the hilum of the ovary with linen suture, according to the Poole technic (Figs. 12 and 13). It is well to bring the height of this

suspension almost level with the round ligament. This procedure prevents the adnexa from prolapsing and becoming adherent in the culdesac and also relieves the congestion due to previous stasis by reestablishing a more normal circulation. A one point suspension of the uterus is performed in order to keep the uterus out of the culdesac.

2. *Implantation Technic.*—The site of the occlusion is again noted by air insufflation and the tube is severed proximal to the occluded area until a free passage of the insufflated air is evident (Fig. 6). The uterine portion of the occluded tube is then freed as far as the cornu from its attachment to the broad ligament, cutting as close as possible to the tube, in order to avoid impairment of the ovarian circulation. Bleeding vessels of the broad ligament are clamped and tied with No. 00 plain gut (Fig. 7). The uterus is firmly held while a specially constructed reaming instrument is passed over the occluded stump of the tube. The tube and its intramural portion is reamed out by a circular movement of the instrument entering the uterine cavity and maintaining as nearly as possible the normal position and course of the
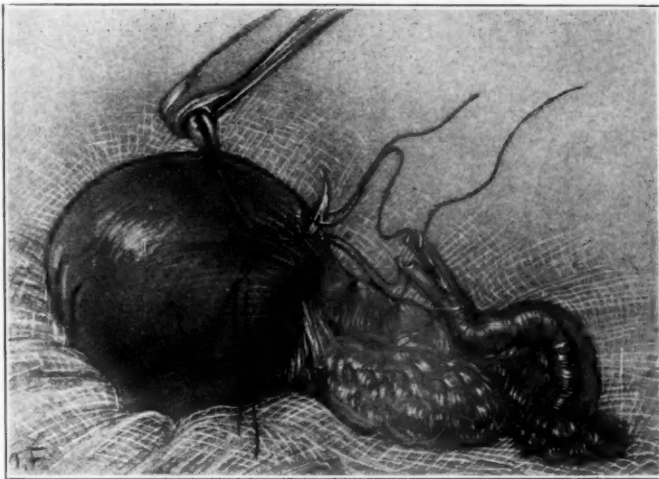
Fig. 10.—Insertion of Reverdin needle 1 cm. beyond center of fundus posteriorly passing out through the newly created uterine opening, in order to bring out the suture previously applied to the end of the superior portion of the bisected tube. The same procedure followed by insertion of the Reverdin needle through anterior surface of the fundus.

tube (Fig. 8). A core remains consisting of the old occluded stump of the tube and the chronically infected cornual tissue which is readily removed when the reamer is withdrawn. The new opening into the uterus will have a diameter of approximately 0.5 cm. This instrument does not produce any free bleeding as might be expected in this area, due to the fact that the circular motion crushes rather than cuts the blood vessels. The slight amount of oozing first noted quickly subsides. The patent portion of the tube is also freed from its broad ligament attachment for a distance of about 0.5 cm., bleeding controlled, and then bisected longitudinally by cuticle scissors, guided by a probe inserted within its lumen (Fig. 9).

Through the superior and inferior ends of the bisected tube a long No. 00 chromic suture is passed and the ends of the suture clamped for further use (Fig. 9). A Reverdin needle is inserted about 1 cm. beyond the center of the fundus, posteriorly, passed out through the newly created uterine opening and the ends of the suture previously applied to the superior bisected portion of the tube reinserted into the eye of the needle, the needle withdrawn, and the sutures brought out on the posterior

surface of the uterus without tension. The same procedure as above is repeated by passing the Reverdin needle through the anterior surface of the fundus and bringing out the suture on the inferior portion of the bisected tube (Fig. 10). The serosal covering of the bisected portion is traumatized and by gently pulling the anterior and posterior fundal sutures, the tube is gradually drawn into the newly created opening and its ends into the uterine cavity. The sutures are then anchored on the fundus and two or three fine supporting sutures are passed through the serosa of both tube and uterus (Fig. 11). The patency of the newly implanted tube is again tested by the use of the insufflation syringe. The reimplanted tube and ovary are suspended by the Poole technic and the uterus by a one point suspension as previously described.

Occlusion may occur at different points in each tube, or there may be an occlusion in one tube at both the inner and outer ends, thus requiring both procedures for proper reconstruction.
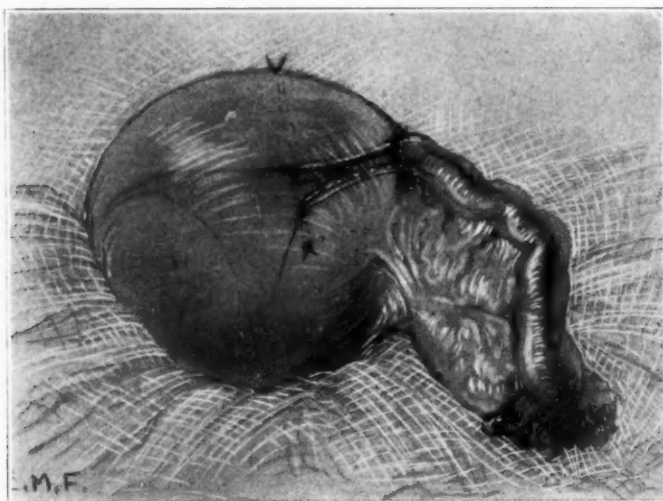
Fig. 11.—By gentle traction on the anterior and posterior fundal sutures on the previously applied anterior and posterior fundal sutures, the tube is gradually drawn into the newly created uterine opening and its end into the uterine cavity. The sutures are then anchored on the fundus. Two or three fine supporting sutures are passed through the serosa of both tube and uterus.

POSTOPERATIVE TREATMENT

Forty-eight to ninety-six hours after operation the patient is subjected to a Rubin insufflation test to determine and maintain patency of the reconstructed tubes. This procedure should not be attempted if any cervical or vaginal plastic operations have been performed or if the patient shows a marked postoperative reaction.

Before the patient is discharged from the hospital this test is repeated to insure the patency of the tubes. If, however, the tubes are patent on discharge from the hospital, patient returns for follow-up at the end of three to four weeks and the patency is again determined by the Rubin test.

Although there has been a minimum of trauma in these operative procedures, sufficient tissue reaction may occur to produce temporary occlusion. It is very surprising that following the heat treatment by the Elliott method, the occluded oviducts again become patent. Therefore the operator should not become discouraged if, upon the discharge of the patient, the tubes appear to be occluded.

A striking example may be cited. One of our cases having extensive pelvic pathology due to postabortal sepsis followed by a marked gonorrheal infection, failed to show patency of the reconstructed tube for a period of eight weeks. Following fourteen Elliott treatments postoperatively, the tubes were shown to be patent both by the Rubin test and a hysterosalpingogram.

For the last six months we have employed the Elliott treatments in all of our cases after discharge, whether the tubes were patent or occluded. This helps to reabsorb any marked tissue reaction following operation.
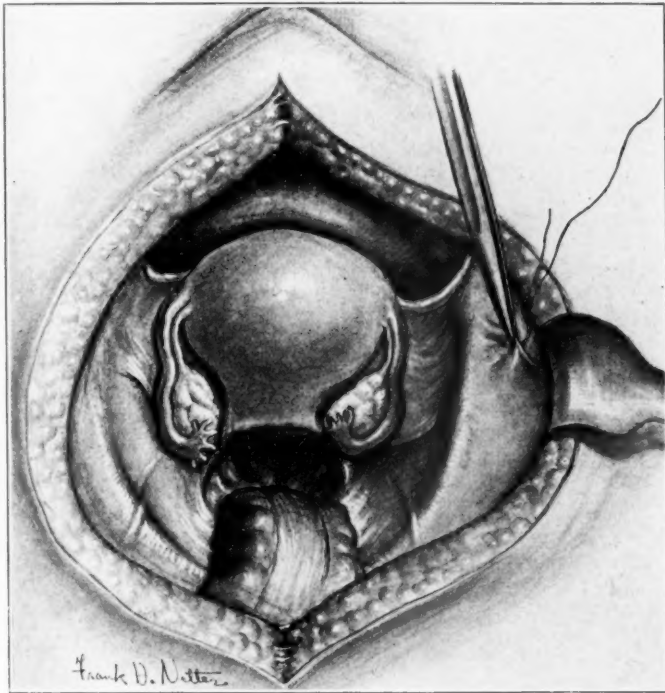
Fig. 12.—Poole's suspension. Suspending tube and ovary from side wall of pelvis. Small bite of peritoneum being taken from side wall of pelvis with linen suture.

POSTOPERATIVE END-RESULTS

Ten patients having bilateral occluded oviducts were studied and operated upon. The diagnosis of occlusion was made in the majority of the cases preoperatively by the transuterine air insufflation method of Rubin, in a few by the hysterosalpingogram, and confirmed in all by the intrapelvic insufflation test as originally suggested by Curtis, at the time of celiotomy.

As previously stated, no special consideration was given to age or marital status in this study. In addition to the tubal occlusions, other pelvic pathology requiring correction in this series of cases was as follows: adherent retroflexion, 5 cases; marked anteflexion, 1 case; dermoid cyst, 1 case; "tary" cyst of the ovary, 2 cases; torsion of a large hydro-

salpinx, 1 case; marked laceration with pseudoadenoma of the cervix, 1 case.

Of the ten patients, seven had a reconstruction operation performed for occlusion of the outer third of the oviduct. These were divided as follows: reconstruction of both tubes, 2 cases; reconstruction of the right tube, 4 cases; the left tube being so diseased as to require removal or having been removed at a previous operation; reconstruction of the
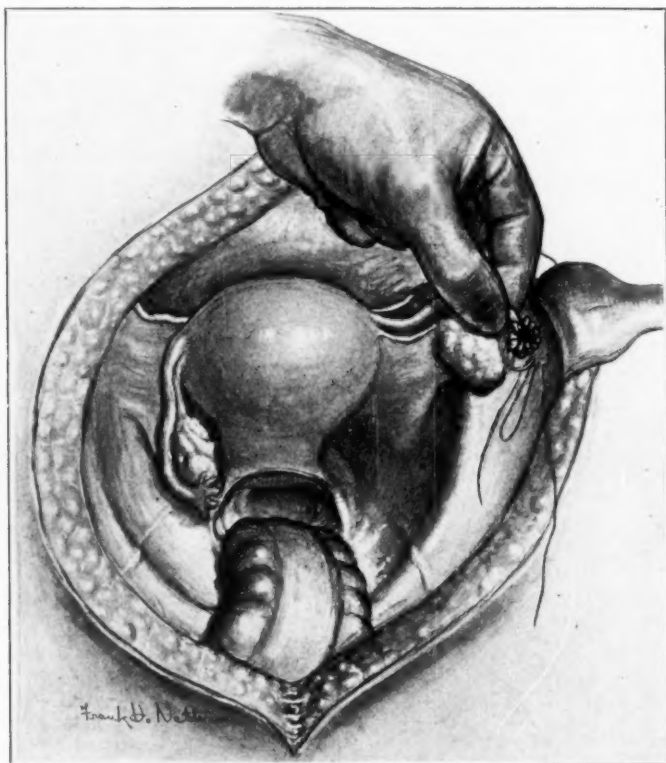
Fig. 13.—Poole's suspension. Small bite taken through hilum of ovary in order to suspend tube and ovary. This suspension prevents tube and ovary from prolapsing into culdesac.

left tube, 1 case, right tube in this case being cord-like and completely occluded.

Five of the above 7 patients having had the so-called "circumcision" operation have patent oviducts as proved by the transuterine insufflation test and by a hysterosalpingogram. It is fair to mention that one of the two cases classified as having nonpatency after operation did not have any tests performed, as these were contraindicated before discharge from the hospital. This patient had an amputation of a markedly infected cervix. She has never returned for examination and cannot be located by our social service.

The remaining three patients of this series of ten had an implantation operation performed for occlusion occurring in the inner two-thirds of the oviduct. These tubes showed a salpingitis isthmica nodosa. The left tube was implanted in one case, the right tube being cord-like in its entire length. The right tube was implanted in the second case, the left tube showing a large hydrosalpinx requiring removal, and in the third case both tubes were implanted.

Two of the implantation cases have patency as proved by the usual tests before mentioned.

In this series of 10 patients having operations performed for occluded oviducts, seven, or 70 per cent, show patency. To correct the statistics by omitting the one patient who failed to return for tests and examination, the percentage of patients showing tubal patency after operation is 77.7 per cent.

As previously stated this study was not primarily instituted as a problem in sterility. It is, however, of interest to mention that one of the patients having an implanted tube became pregnant three months after operation, and had a normal delivery of a full-term, viable child. And another having had a reconstruction of the outer third of both tubes is now three months pregnant, fourteen months after operation.

SUMMARY

1. Tubal occlusions for the purpose of this study were classified as those occurring in the outer third of the tube, and those occurring in the inner two-thirds of the tube.

2. Two distinct operative procedures were instituted for reconstruction.

3. The so-called circumcision operation was performed for occlusions occurring in the outer third of the tube.

4. The implantation operation was performed for occlusions occurring anywhere in the inner two-thirds of the tube.

5. Seven of the 10 patients operated upon, or 70 per cent, have patent tubes after operation. The corrected percentage of patency after operation is 77.7 per cent.

REFERENCES

Meaker, S. R.: Am. J. Obst. & Gynec. **20**: 6, 1930. *Sovak, F. W.:* Am. J. Obst. & Gynec. **23**: 4, 1931. *Curtis, A.:* Text-book of Gynecology, Air Inflation of the Tube, p. 233, 1930. *Cotte, G., and Bertrand, Pierre:* Gynec. et Obst. **15**: 182-195, 1927. *Unterberger, F.:* Monatschr. f. Geburtsh. u. Gynäk. **73**: 1-4, 1926. *Kennedy, W. T.:* J. A. M. A. **85**: 13-16, 1925. *Kerwin, W.:* Am. J. Obst. & Gynec. **16**: 641, 1928. *Rubin, I. C.:* New York State J. Med. **29**: 379, 1929. *Schmitz, H.:* Am. J. Obst. & Gynec. **23**: 47, 1932. *Holden, F. C., and Gurnee, W. S.:* Am. J. Obst. & Gynec. **22**: 87, 1931.

59 East Fifty-Fourth Street.

117 East Seventy-Second Street.

CHEMICAL CHANGES IN THE PARTURIENT'S BLOOD*

H. W. Siedentopf, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, University of Chicago, and the Universitäts-Frauenklinik, Leipzig, Germany)

CHEMICAL research in gynecology and obstetrics deals with a very unusual situation. During menstruation, pregnancy, labor, and puerperium, the blood chemistry of the woman is normally and regularly changed, in comparison with the normal average findings. These phases are most important and frequently lead to pathologic changes. We must, therefore, determine the normal condition during these certain phases of the sexual life of the woman, before undertaking the investigation and explanation of pathologic deviations.

Our knowledge today concerning these normal changes is still quite incomplete. Much work has been done on the normal physiologic chemistry of pregnancy, but even here there are many disagreements. Our knowledge of the norn.al chemical changes, which are brought about by labor in the body of the mother, is much more incomplete. Labor is an event of such decisive effect that we must expect considerable change in the chemistry of the body. Careful investigation in this direction seems to be absolutely necessary.

Most investigators have restricted themselves to one or, at the most, two series of observations during labor and have called their findings "the general labor value." Very soon after the beginning of our work we found that labor could not be comprehended as a uniform event from the chemical viewpoint. During the different stages of labor varying changes take place in the body chemistry of the mother.

Labor is usually divided in the physidlogic sense into the following stages: (1) Dilatation, (2) expulsion, and (3) placental stage. We have found that this division does not apply to the chemical changes. The changes which take place during the first stage of labor and the longest part of the second stage (second A-stage) are less marked than those that take place during the last minutes of the expulsion stage. This part, which we will call the second B-stage, is the actual time of real birth, from the appearance of the head in the introitus to the complete expulsion of the child.

Every stage of labor must be investigated separately in order to grasp the changes which occur during it. A more thorough and separate investigation of the second B-stage was undertaken. The first stage and the second A-stage were studied together. Of course, a separate investi-

---

*Read, by invitation, before the American Gynecological Society, May 30 to June 1, 1932, at Quebec, Canada.

gation would be more desirable. Thus, our experiments were divided into four parts:

I First and second A-stage of labor.
II Second B-stage of labor.
III Third stage of labor.
IV Investigation of the puerperium during the fifth or
    sixth days postpartum.

Furthermore, normal nonpregnant women were investigated as controls.
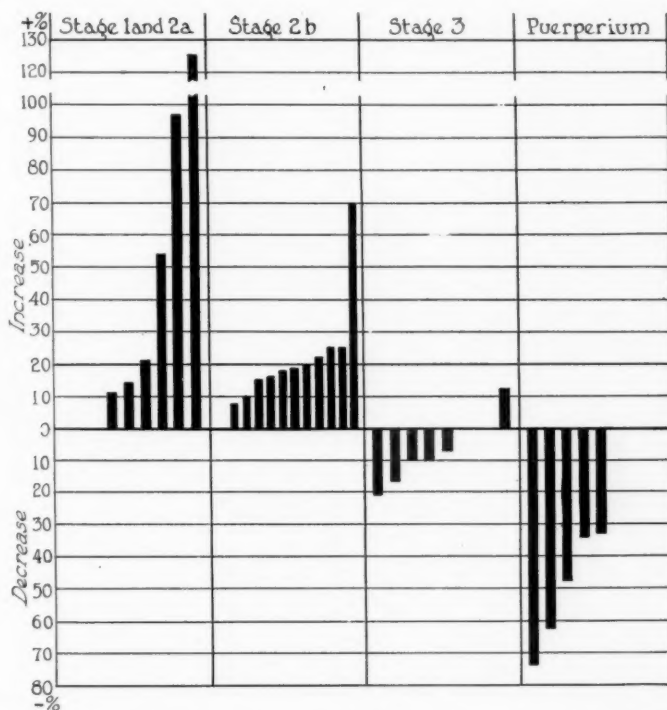
Fig. 1.—Changes in the acetone content during labor expressed in percentage.

The investigations included only absolutely normal parturients who received no medicine or anesthesia of any kind. The blood was taken from the cubital vein without compression. The most reliable technic was used and the blood examined for the amount of ketone bodies (acetone, diacetic acid, and β-oxybutyric acid), nonprotein nitrogen, blood sugar, hydrogen ion concentration, water content, dry residue, total nitrogen, refraction, etc. In some cases the urine was also examined.

To determine the ketone bodies, a procedure which was quite similar to the Engfeldt method was used. In nine normal cases investigated for control, we found acetone, 1 to 1.57 mg. per cent, and β-oxybutyric acid, 5.75 to 11.75 mg. per cent. These amounts corresponded to the findings of other authors.

Figs. 1 and 2 show the changes which occur in the *acetone and β-oxy-butyric acid* content of the blood during the different stages of labor. They represent graphically the four different parts of the investigation mentioned above.   The effect of every phase was investigated separately by taking one specimen of blood at the beginning and another at the end of the phase.   In the charts the absolute height of the finding is not re-ported, but the relative changes which occurred during the different phases are expressed as percentage of the first value (the value found at the beginning of the phase).   Each column represents one case.   The
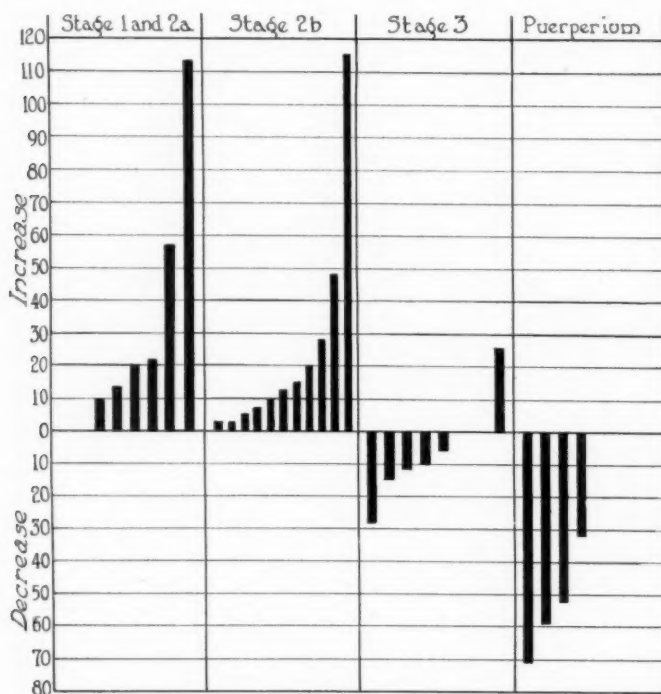
Fig. 2.—Changes in the β-oxybutyric acid content during labor expressed in percentage.

downward trend designates a decrease and the upward an increase.   The effect of labor upon the acetone and β-oxybutyric acid contents is very significant, as is shown by the illustrations.

In Part I of the investigation, the first blood specimen was taken at the beginning of labor and the second immediately before the birth of the child.   During the stage of dilatation and the first part of the expulsion stage, an increase of the acetone and β-oxybutyric acid content of the blood occurred in all cases.   In some the first value was doubled.

Part II concerns itself with the delivery of the child (second B-stage). The first specimen of blood was taken just before the head passed through the introitus, and the second immediately after the birth but before the umbilical cord was tied.   The average interval between the two veni-

punctures was only nine minutes, the longest time being sixteen minutes and the shortest four minutes. The figures show that as marked increases occurred in most of the cases during this short time as during the period of several hours in Part I of the investigations. The comparison of time indicates that something entirely different must have taken place during the few minutes in Part II than in the number of hours in Part I. The influences effecting the blood chemistry during the second B-stage of labor are, therefore, not merely a continuation of those operating in the first and second A-stage.

Part III comprises the placental stage. The first specimen of blood was taken immediately after the birth of the child and the second after the expulsion of the placenta. Here the tendency towards a decrease in the amount of ketone bodies in the blood predominated.
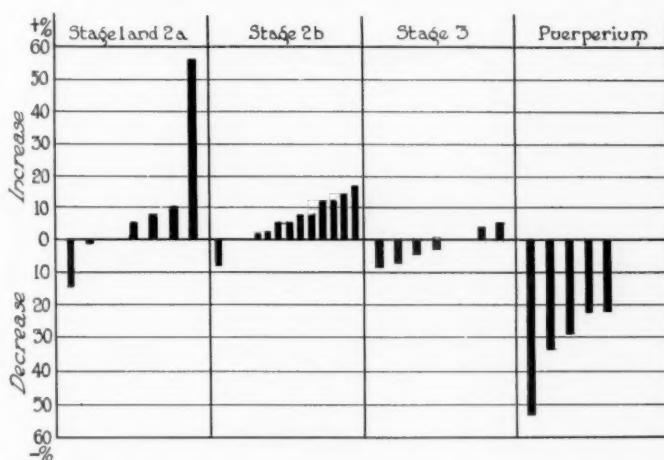
Fig. 3.—Changes in the blood-sugar content during labor expressed in percentage.

During Part IV, comprising the puerperium, a marked lowering of the values of acetone and β-oxybutyric acid was seen. The absolute values found in the puerperium corresponded with the general normal average. Therefore, the marked decrease is a sign that the values during labor are considerably higher than the normal values in nonpregnant patients.

The blood sugar was determined by the method of Hagedorn-Jensen. In twelve normal nonpregnant cases, from 74 to 97 mg. per cent of blood sugar were found, which corresponded to the normal average.

Fig. 3 shows the changes in the amount of blood sugar. They are not as uniform as those of the other mentioned substances. From this, perhaps, one may conclude that the changes in the blood sugar during labor are due to more varied influences than those of the ketone bodies. During the dilatation stage and the first period of expulsion, we found both an increase and a decrease, the increase predominating. The case with

a marked decrease showed also other deviations. The delivery of the child was, in most instances, associated with an increase in the blood sugar. Varying and weak influences seemed to effect the blood sugar during the placental stage, giving slight increases or decreases. The remarkable decrease during the purperium, shown in the fourth part of Fig. 3, proves that during labor the values must have been relatively high.

The nonprotein nitrogen was determined with the Kjeldahl method. In nine normal nonpregnant cases we found from 19.6 to 40.0 mg. per cent. Fig. 4 shows the changes during labor. During Part I, a marked increase took place in most of the cases. During Part II (second B-stage), the rise predominated. A decrease occurred in most of the cases
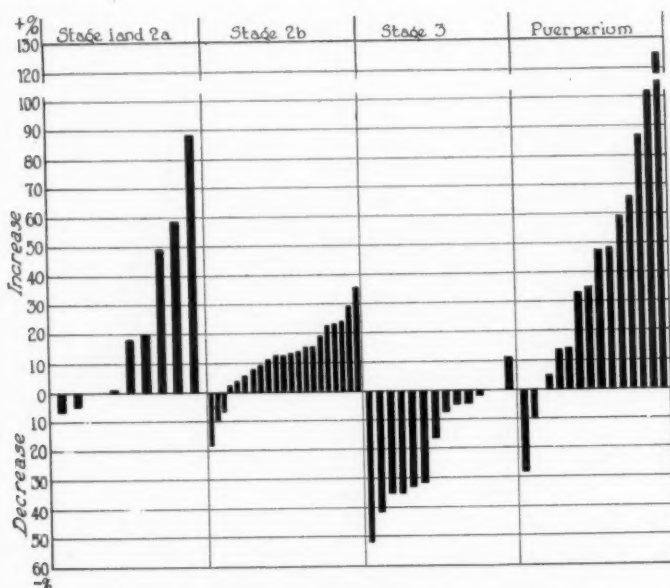
Fig. 4.—Changes in the nonprotein nitrogen content during labor expressed in percentage.

during the placental stage. A very marked increase could be seen again during the puerperium. The two exceptions may be partly explained by the fact that these cases had very high values during labor.

Fig. 5 illustrates the changes in the hydrogen ion concentration. It is drawn upon another principle than the preceding figures, the changes being noted in absolute values and not expressed in percentages. About 400 determinations of P_H were included in this chart, which made it impossible to sum them up singly. Therefore, the average values are given, but variations from the average were extremely rare.

The horizontal lines correspond to the values of the P_H at 38° C. The shaded zone between $P_H = 7.37$ and $P_H = 7.40$, shows the sphere of the values found in 23 normal nonpregnant women. All P_H determinations were made with the electrometric method.

The curve is divided vertically into three sections: Pregnancy, labor, and puerperium. Pregnancy was included in the P_H examinations because we have done special work on this subject and have obtained results which are different from those of former investigators.

According to the older literature the augmentation of acids in the blood during pregnancy was an absolute certainty. Later, following the articles of Hasselbalch and Gammeltoft, the doctrine of the "compensated acidosis of pregnancy" was universally accepted. This theory was included in every textbook, but the differentiation between actual and compensated acidosis was not always very clear. Insufficient attention has been given to the investigations of Michaelis, who examined the blood
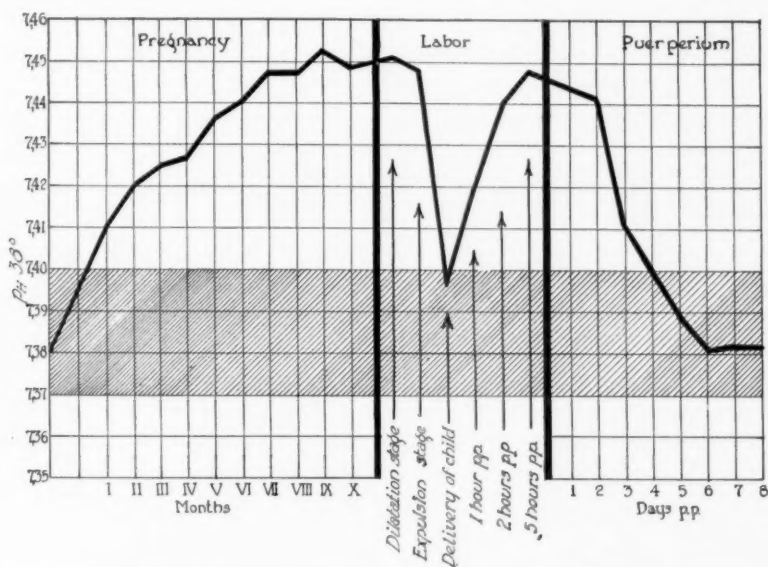
Fig. 5.—The hydrogen ion concentration during pregnancy, labor, and puerperium.

P_H in some cases of pregnancy with the electrometric method, and found a slight shifting to the alkaline side. Later Bock, using the same method, noted a slight shifting to the acid side. To clarify this question, Eissner and the author made electrometric P_H determinations in a large number of cases. We proved that there is at least no actual acidosis.

In the German literature, the doctrine of acidosis of pregnancy, at least of a compensated one, still holds. Recently Anselmino acknowledged a slight actual alkalosis of pregnancy, but believes that there is, in spite of this, a compensated acidosis. He states further that he could prove an augmentation of unknown acids in the blood during pregnancy by electrometric titration.

In the American literature, the doctrine of acidosis of pregnancy seems to have lost ground for a longer period of time. For instance, Kydd states that there is no "acidosis of pregnancy." He found that the un-

known acids were not increased during pregnancy, as did also Oard and Peters. Marrack and Boone have proved a shifting of the P_H to the alkaline side by colorimetric investigations.

Other English and American authors have also made determinations of the P_H during pregnancy, but, in spite of the results, Oard and Peters wrote as follows in 1929: "P_H determinations on sera in pregnancy by methods of sufficient accuracy are as yet not available in the literature." Our investigations, of which the results are reproduced in the illustrations under discussion, should be sufficient to supply this lack.

As shown in Fig. 5, the value of the P_H is higher even in the first month of pregnancy than in the normal nonpregnant cases. This increase continues with little variation until the ninth month, which means progressive shifting to the alkaline side up to this time. The slight decrease during the tenth month is probably due to the beginning of the first weak uterine contractions.

During the stage of dilatation we find approximately the same value as during the last month of pregnancy. During the expulsion stage only a very slight shifting to the less alkaline side becomes apparent; so up to the very last moment of labor there is no considerable change in the actual P_H of the blood, in spite of all labor pains.

At the very moment of birth a sharp decrease takes place. Within a few minutes a change towards the acid side occurs, which is seven times greater than that which took place during the hours or even days of labor. This shifting persists for a remarkably long time. It takes five hours before the P_H returns to the average value which existed during the first stages of labor.

TABLE I. COMPARATIVE VALUES OF THE P_H DURING THE DILATATION STAGE, IMMEDIATELY BEFORE AND AFTER BIRTH OF THE CHILD

NO.	NAME	AGE	TIME OF FIRST VENIPUNCTURE BEFORE BIRTH	TIME OF SECOND VENIPUNCTURE BEFORE BIRTH	TIME OF THIRD VENIPUNCTURE AFTER BIRTH	1. VAL	2. VAL	3. VAL
1	R	24	14 Hr. 9 Min.	2 Min.	4 Min.	7.44	7.44	7.39
2	Sch	24	5 Hr. 22 Min.	1 Min.	3 Min.	7.43	7.42	7.38
3	F	34	9 Hr. 5 Min.	2 Min.	2 Min.	7.45	7.44	7.39
4	R	23	1 Hr. 9 Min.	1 Min.	4 Min.	7.44	7.43	7.39
5	H	20	6 Hr. 11 Min.	5 Min.	3 Min.	7.44	7.44	7.39
6	K	23	9 Hr. 38 Min.	4 Min.	2 Min.	7.46	7.45	7.40
7	M	27	4 Hr.	5 Min.	4 Min.	7.45	7.45	7.40
8	W	22	6 Hr. 32 Min.	2 Min.	9 Min.	7.45	7.44	7.39
9	L	26	4 Hr. 23 Min.	2 Min.	2 Min.	7.46	7.45	7.40
10	H	20	7 Hr. 54 Min.	2 Min.	4 Min.	7.45	7.45	7.39

During the puerperium we observed a slow decrease to the values found in nonpregnant women. The most remarkable finding was that the P_H during the first days postpartum was the same as during pregnancy, and the actual reaction did not return to the normal value until several days later.

Fig. 5 shows average P_H values. Table I indicates that every single case followed the same rule. The first blood specimen in these cases was taken at the beginning of labor, the second immediately before, and the third immediately after the birth of the child. The findings show that there is very little or no shifting in the P_H value during the time of dilatation and the second A-stage, but that a sudden marked change to acid takes place during the time of the actual birth of the child.

The other blood examinations, total nitrogen, reflection index, erythrocyte count, etc., were done in order to investigate the changes in blood concentration during labor. The result was as follows: During Part I of the experiments, the dilatation stage and the main part of the expulsion stage, an increase of the concentration was found. During the period of the actual delivery of the child a marked decrease in the concentration of the serum took place. An even more marked decrease occurred during the placental stage.

We will now consider briefly the theories for the changes found in the different periods of labor.

In Part I of the investigations, that is, during the first and second A-stage of labor, we have observed the following: Marked increase of acetone and β-oxybutyric acid, increase of blood sugar in most cases, increase of nonprotein nitrogen in nearly all cases, no marked change in the hydrogen ion concentration (a most interesting fact), and slight concentration of the blood.

An explanation of these changes presents some difficulties, because they occur over a long period of time, in which many accidental influences may take place. The most interesting observation is a negative finding, namely, the lack of change of the P_H. The intensive muscular work should produce a large amount of acid. Indeed, several investigators found a marked increase in the amount of lactic acid. An augmentation of the acidic ketone bodies has been proved by us. The organism, however, is able to neutralize and eliminate entirely all these acids during the whole course of labor up to the very last stage. We found a remarkable acidification of the urine during labor as a result of this elimination.

The increase in the amount of ketone bodies may be best explained by the insufficient nutrition of the parturient, in connection with the strong muscular efforts.

The increase of the blood sugar is probably due to nervous influences, especially an irritation of the sympathetic system. Endocrine disturbances, with eventual increase of adrenalin in the blood, probably assist in this phenomenon. Furthermore, the increase of lactic acid and ketone

bodies raises the amount of blood sugar. There is no reason to believe that the elevation of the blood sugar during labor is a sign of hepatic change, which is the opinion of some authors.

The increase of nonprotein nitrogen, after considering all possible explanations, is probably due to a slight retardation of the renal function during labor.

The concentration of the blood must be traced back to the muscular effort and the loss of water by perspiration, respiration, etc.

On the whole, we have observed that the changes which occur in the maternal body during the hours or even days of the first and second A-stage, are not extremely marked. It is all the more surprising that during the brief second B-stage, much more marked changes take place in the substances investigated. The comparison of time alone proves that it is impossible to consider these last minutes of labor as a simple continuation of the long first and second A-stage. It is impossible to explain the changes that occur by an accentuation of labor pains at the very end of labor. Even if there were some extremely strong pains they could never bring about more changes than the entire preceding period of labor. We, therefore, believe that during the real delivery of the child new and important influences are at work. The following changes were noted during this stage of labor: Marked increase of the ketone bodies, increase of blood sugar, elevation of the nonprotein nitrogen, enormous shifting of the blood P_H to the less alkaline side, and slight dilution of the blood.

These findings and the short time in which the changes occurred, suggest the opinion that there is a sudden influx of acid substances in the blood during the real delivery of the child from some repository. We believe that the sudden reduction in size of the uterus is the main cause. Through reduction the blood and lymph fluid, which is contained in the uterine wall and the intervillous space, is pressed out and brought into the general circulation. In consequence of the labor pains and the metabolism of the fetus, this fluid contains many by-products of metabolism, most of them acid in character. This theory may be proved by the conduct of the different substances.[1]

During the *placental stage* the following changes were observed: Decrease in the ketone bodies, no uniform behavior of the blood sugar, decrease of the nonprotein nitrogen, no change of the P_H or a slight shifting to the alkaline side, and marked dilution of the blood.

The explanation is simple. The main factor in this change is the loss of blood and its consequent dilution by tissue fluid. Another part is the after-effect or retrogression of the labor changes. The fact that there are several antagonistic influences present explains the lack of uniform changes in this stage of labor.

During the puerperium there was a marked decrease of the amount of

---

[1]*Siedentopf, H.:* Die Physiologische Chemie der Geburt. Ambrosius Barth, Leipzig, 1932.

ketone bodies and blood sugar, an increase of the nonprotein nitrogen, and a gradual lowering of the hydrogen ion concentration.

These changes indicate the gradual return of the organism to the normal nonpregnant state. The most interesting part of this phenomenon is that it takes several days and, as other investigations show, even months, until this return to normal is completed. So the changes during pregnancy, such as the alkalemia, cannot be due alone to direct influences of the fetus and the placenta.

REFERENCES

Anselmino: Die Regulation des Säure-Basenhaushalts in der Schwangerschaft. Supplement VI. Monatschr. f. Geburtsh. u. Gynäk., 1932. *Anselmino and Hofmann:* Arch. f. Gynäk. **140**: 373, 1930. *Behrend, Berberich, and Eufinger:* Arch. f. Gynäk. **143**: 537, 1931. *Cantarow, Montgomery, and Bolton:* Surg. Gynec. Obst. **51**: 469, 1930. *Dieckmann and Crossen:* AM. J. OBST. & GYNEC. **14**: 3, 1927. *Jarcho:* AM. J. OBST. & GYNEC. **17**: 13, 1929. *Kydd:* J. Biol. Chem. **91**: 63, 1931. *Marrack and Boone:* Brit. J. Exper. Path. **4**: 261, 1923. *Oard and Peters:* J. Biol. Chem. **81**: 9, 1929. *Oberst and Plass:* J. Biol. Chem. **92**: Nos. 13 and 14, 1931. *Siedentopf:* Die Physiologische Chemie der Geburt, Leipzig, 1932. *Siedentopf and Eissner:* Ztschr. f. Geburtsh. u. Gynäk. **46**: 76, 1929. *Stander:* Bull. Johns Hopkins Hosp. **35**: 133, 1924. *Stander and Cadden:* Bull. Johns Hopkins Hosp. **47**: 382, 1930. *Williams and Wills:* Quart. J. Med. **22**: 493, 1929.

DELIVERY THROUGH A SPURIOUS BIRTH CANAL[*]

RALPH A. HURD, M.D., F.A.C.S., NEW YORK, N. Y.

A PRIMIPARA at term was successfully delivered of a six pound infant after a labor of twenty-four hours. The membranes ruptured spontaneously two hours after the onset of pains, and it was a vertex presentation which began as a posterior and rotated naturally to the left anterior position. The feature of this case relates entirely to the cervix and the unusual mode of dilatation which occurred. She was examined three times rectally and once vaginally immediately before removal to the delivery room where labor was terminated by medium episiotomy and low forceps. Immediate examination of the cervix showed that the external os was intact and that the child had delivered through an artificially created passage in the posterior wall of the cervix at or near its middle third. The descending head apparently had impinged upon this area of the cervical canal so vigorously and had compressed it to such thinness as to force it to give way. The aperture thus created was closed with interrupted catgut sutures but unfortunately union failed to occur. Inspection of the cervix several months postpartum revealed nothing unusual in its appearance, but when pulled forward so as to expose its entire posterior aspect, the accessory birth canal could be demonstrated as a cervico-vaginal fistula, and a sound could be passed through the real external os, into the true cervical canal and out again into the posterior vaginal fornix. Here then is a woman who was not examined vaginally until the very end of a twenty-four-hour labor, and in whom, possibly because of this, the obstetrician failed to recognize an abnormal situation which conceivably might have been averted with the more accurate information obtainable by vaginal palpation.

37 EAST SIXTY-FOURTH STREET.

CONSIDERATION OF A NEW VIEWPOINT ON THE ETIOLOGY OF RENAL TUBERCULOSIS IN WOMEN*

GUY L. HUNNER, M.D., BALTIMORE, MD.

AT THE beginning of the present century the medical profession was fairly well informed on the desirability of early diagnosis and radical surgery in renal tuberculosis. And yet in spite of the great advances in urology since that time, our views concerning the etiology and therapeutics of renal tuberculosis have changed but little.

Some of you may remember that about thirty years ago there was prevalent an idea that renal tuberculosis in women occurred more frequently in the right than in the left kidney. It was thought that the greater mobility of the right kidney interfered with its drainage and thus favored a more frequent incidence of tuberculosis on this side.

In September, 1903, I read a paper before the Medical and Chirurgical Faculty of Maryland on "Tuberculosis of the Urinary System in Women,"[1] reporting on 35 cases which had occurred in the service of Howard A. Kelly and his associates in Baltimore. In this list of 35 patients 17 were operated upon for tuberculosis of the right kidney and 18 for tuberculosis of the left, 5 of the series probably having bilateral renal tuberculosis. This experience seemed to explode the theory that the disease occurs more frequently on the right side because of impaired drainage.

In spite of the more recent work on ureteral stricture, showing the influence of interference with drainage on practically all of our so-called surgical diseases of the kidney, it was not until about seven years ago that my attention was again called to the possibility that defective drainage might have an important etiologic bearing on renal tuberculosis. My first report on a series of stricture cases was entitled, "Stricture of the Ureter, Excluding Tuberculosis and Calculus; Report of Fifty Cases."[2] I soon found that our former ideas concerning the sequence of events in the formation of ureteral stone and its surrounding infiltration with inflammatory tissue were probably erroneous, and two years later I published arguments to show that in most instances the ureteral stricture is primary and the encased stone secondary.[3] Since then I have published a number of articles containing facts which seem to demonstrate that one cannot discuss the etiology of calculus of either ureter or kidney without a full consideration of ureteral stricture.

More recently facts have been accumulating to demonstrate that the title of my first report on ureteral stricture is further subject to criticism because of its implication that the type of stricture under discussion was not associated with tuberculosis of the upper tract. Up to the present time we have all taken it for granted that the frequent obstructive conditions found in the ureter in association with renal tuberculosis are specific in nature and are directly derived from the diseased kidney.

In about 1925, or nine years after my first publication on ureteral stricture, I became gradually impressed by the fact that I was seeing a considerable number of patients who had undergone a nephrectomy for tuberculosis, and who had returned months or years later because of

symptoms referable to the remaining kidney. On going over history records I was surprised to find that I had been consulted by 15 patients belonging in this category. Since 1925 two more of our former patients who have had nephrectomies have returned because of stricture symptoms on the other side. In 2 of these 17 cases the symptoms were apparently due to a wide open ureteral orifice and free reflux of urine from the bladder to the kidney, causing renal pain as the bladder and upper tract became distended. Both of these patients had been under my care for a monolateral renal tuberculosis, and at that time had been found to have extensive inflammatory involvement about the base of the bladder, and I attributed the subsequent loss of the valvular control of the ureter to the action of scar tissue after healing of the bladder had taken place. Whether these two patients had originally had ureteral stricture could not be determined because of the widely dilated ureteral lumen at the time of final consultation.

In the other 15 patients we found, on their return, no evidence of infection in the remaining kidney, and their symptoms were apparently due to ureteral stricture as determined by the bulb test, pyeloureterograms, and the satisfactory results of treatment by simple dilatation.

These experiences gradually forced the question: were these strictures present on the supposedly normal side at the time of the removal of the other kidney for tuberculosis? We know that simple ureteral stricture is practically always bilateral, and we know that serious damage from stricture may result to both kidneys without a complaint of any kind. We also know that the patient with bilateral stricture may localize the symptoms on one side, while investigation shows the symptomless side to be the one more damaged. Hence it must be insisted that absence of symptoms on the supposedly normal side at the time of a nephrectomy for tuberculosis does not preclude the presence of ureteral stricture on this side. An occasional patient with unilateral tuberculous kidney complains of pain only on the nontuberculous side. In some cases careful anamnesis reveals a complaint of pain or soreness in the region of the good kidney, while with accurate physical examination one is surprised at the high percentage of patients who have on the supposedly normal side tenderness in the kidney region and over the ureter at the pelvic brim and in the broad ligament region.

On going back to the records of some of our former tuberculosis patients in whom urograms had been taken on both sides, we were surprised to find the evidences of dilatation on the supposedly normal side, thus demonstrating that much of our routine work in medicine is performed with eyes that perceive but with minds that are slow of apperception.

We see cases of renal tuberculosis in which the history of symptoms, the clinical examination, and the final examination of the removed kidney all suggest that the patient may have had a hydronephrosis or cal-

culus formation, and therefore ureteral stricture, for a long period before the onset of the tuberculosis.

The above considerations led to the deliberate investigation of all cases of renal tuberculosis for the possible presence of bilateral stricture. We have seen only 12 proved renal tuberculosis cases since undertaking this investigation. Two of these patients had bilateral renal tuberculosis and bilateral ureteral stricture, and of course these strictures may have been secondary. One had undergone a left nephrectomy for tuberculosis, and we found advanced renal tuberculosis of the remaining kidney with two ureteral stricture areas and a stone in the upper stricture. The other nine patients had clinical evidence of tuberculosis on one side only, but they all had bilateral stricture.

Twelve cases are far too few from which to draw convincing conclusions, but the fact that careful investigation has demonstrated bilateral stricture in every case (except in the one with the unilateral kidney) is suggestive that this is a field worthy of further study.

We are cognizant of the many pitfalls in the diagnosis of tuberculosis of the kidney, and we have not the space to discuss them here; but for all practical purposes when we can demonstrate that one kidney is doing the better work and that it repeatedly yields a urine free from leucocytes, we may consider this kidney to be nontuberculous.

Space forbids a review of all these cases and we will first present the illustrations with brief notes on three patients to demonstrate some of the interesting problems growing out of a special study of this character. To save space urograms of the tuberculous kidney are omitted.

Case A.—Fig. 1 is from a patient thirty-eight years of age, who, until a short time before she came to us had always enjoyed exceptional health. In spite of recent complaints she had gained in weight, in the five years previous to admission, from 165 to 180 pounds. There had never been signs or symptoms of lung trouble except for one or two brief attacks of bronchitis. There had been occasional attacks of sore throat and frequent colds, and the tonsils were considerably enlarged and cryptic.

Symptoms probably due to ureteral stricture began about ten years previously as evidenced by an increasing dysmenorrhea accompanied by dull aching and pain in the right side. The youngest of her two children was then five years of age and her menstrual periods had always been normal and free from pains. For several years the symptoms were diagnosed as due to "ovarian trouble," and three years before she came to us she was advised to have an operation for appendicitis. During the past three years there had been about 12 attacks of quite severe right upper quadrant pain accompanied by nausea and vomiting, and followed by a day or two of soreness in the right flank. During the attack, and for twenty-four hours following, voiding was more frequent and slightly painful. There had been no bladder symptoms between attacks until recently. She had never seen blood in the urine. She thinks there had never been fever.

For six months before admission the bladder symptoms had become constant and severe, and she often voided eight times at night. With this constant bladder misery the pain and soreness in the right flank had also become constant and spread across the abdomen.

The patient entered the Woman's Hospital Dispensary in February, 1927, and the resident surgeon, being unable to catheterize the ureters, asked me to see the patient with him on March 1. There was great tenderness over both ureters in the broad ligament region, and palpable infiltration in the region of the right, but the ureter could not be outlined. The bladder showed considerable ulceration suggestive of tuberculosis. The right ureteral orifice region was granular, red and edematous and a catheter would not enter for more than 1 to 2 cm. On subsequent visits we were able to catheterize the left ureter which was found to have dense strictures and the resident finally got this side dilated to a 16 Fr., the patient steadily improving in her general health and the bladder symptoms lessening under the ureteral and local bladder treatment. The bladder urine showed considerable pus but a negative culture. The urine from the left kidney was normal. A half-hour intra-
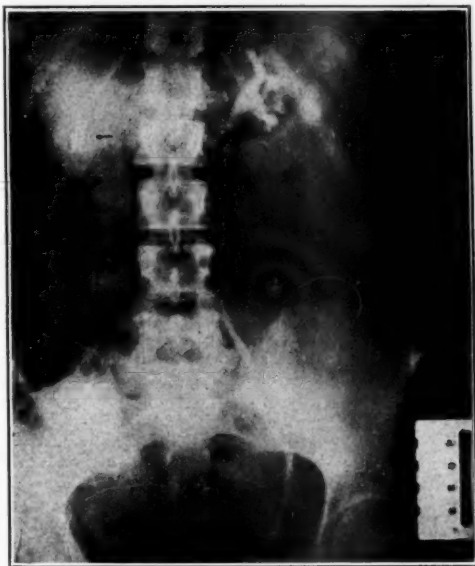
Fig. 1.—Showing a rather large left kidney shadow with apparently normal pelvis and calices. Left ureteral lumen about normal, but the original film shows two definitely narrowed areas, one in the iliac gland region and one in the juxtavesical region. These x-ray narrowings correspond to two areas of hang obtained by the dilating bulb. Note the rather long liver lappet. Right kidney shadow small. An irregular shadow in lower pole region measuring about 4 cm. by 15 mm., apparently made up of numerous small porous stone shadows. This appearance together with the position relative to the liver aroused suspicion of possible gallstones.

venous phenolsulphonephthalein test showed 33 per cent from the left and about 4 per cent through the bladder from the right kidney. Many slides stained for tubercle bacilli and one guinea pig injection were all negative.

Because of the great improvement under treatment of the left ureteral strictures and because tubercle bacilli could not be demonstrated, we hoped that the case might prove to be one of simple stricture resulting in stone formation in the right kidney; but on the strength of the urinary findings of pus and a negative culture, the appearance of the bladder and the x-ray findings (Fig. 1), suggesting calcareous deposits rather than true stone formation, we diagnosed right renal tuberculosis and I assisted the resident in a nephrectomy on June 16. The opened kidney showed a thin cortex, its upper and middle calices holding large tuberculous abscesses and considerable calcareous material. The patient was followed for seven months with

occasional bladder treatments and she was finally discharged as well January 10, 1928.

CASE B.—Fig. 2 is the urogram of the right side of a girl whose left tuberculous kidney was removed in November, 1925, and whose subsequent history strongly suggests that she belongs in the class of patients who originally have simple bilateral stricture and elusive ulcer of the bladder secondary to a focal infection area.

H. P., aged thirteen years, admitted to the Harriet Lane Home July 25, 1925, because of bladder symptoms of three months' duration, and recent hematuria. There had been but little pain but the patient had nocturnal and diurnal incontinence, the leakage occurring at times as often as every half hour and at times lasting continuously for several minutes. There had been bloody urine on two occasions ten and two days before admission. Examination of heart, lungs, and abdomen

Fig. 2.—Right urogram after left nephrectomy, catheter out. Note the slightly dilated kidney pelvis with dilated upper and lower calices fused with the pelvis. Slightly dilated ureter except in the two stricture areas in the iliac gland and broad ligament regions. Note the large shadow on the left just above the sacrum, calcareous deposits in the lumbar gland region.

negative. "Ragged" tonsils. Tuberculin test 0.10 mg., positive. Catheterized urine: many motile bacteria, many erythrocytes and leucocytes. The patient was transferred to the gynecologic service August 7. Cystoscopy showed almost universal inflammation of the bladder; a culture produced S. albus and B. coli. Urinary antiseptics by mouth. Frequent rises in temperature.

On October 19 a guinea pig previously inoculated with bladder urine was reported as dead from tuberculosis. On October 27 the patient was cystoscoped under general anesthesia and bilateral ureteral stricture was found, with normal urine from the right and creamy purulent urine from the left kidney. A urogram from the left showed almost universal etching out of the calices, and large calcareous masses in the region of the left lumbar glands.

Left nephrectomy October 31, 1925. Discharged November 24, with normal temperature and marked general improvement but with only slight change in the urinary frequency and incontinence. Placed under the care of a district nurse, who gave instillations twice a week of 1:10,000 bichloride solution, one ounce left

in the bladder. This treatment was continued for about one year, the bladder symptoms gradually lessening and cystoscopy showing marked improvement. In May, 1927, the patient reported that she had no more bladder pain, slept so soundly at night that she did not awaken, but wore a pad for the incontinence. Voided every two to three hours in the day, and had frequent incontinence. Considerable pain at times in the upper right flank. The bladder appeared normal except for a few slightly congested areas in the vertex. We then began occasional dilatation of the right ureter, seeing the patient at intervals of a few months, and by the Christmas holidays, 1928, the ureter was taking bulbs of 5.6 mm. (17 Fr.). The bladder appeared normal except for a tiny area in either side of the vertex which looked typical of elusive ulcer. The wide dilatation of the ureteral strictures having failed to cure her incontinence, we tried thorough fulguration of the ulcer areas under ether anesthesia December 22, 1928. This seemed to improve her condition somewhat but on April 20, 1929, we again began a series of ureteral dilatations and by June 1 had the strictures again taking a 17 Fr. bulb. The incontinence still persisting, we fulgurated a second time on June 20, 1929. This seemed to have no marked effect and we took up the occasional dilatations again in October. In April, 1930, the tonsils were removed and the patient's incontinence soon began to improve. She had 7 ureteral dilatations in the next year and on March 14, 1931, she was discharged as well. At that time she was having no discomfort in the right flank; she sometimes voided once during the night, but never had incontinence. Careful search of the entire bladder showed a normal or slightly scarred condition in the two vertex areas.

The discovery that bilateral simple stricture of the ureter probably antedates tuberculosis of the upper tract in a large proportion of all cases of urinary tuberculosis possibly offers an explanation for many troublesome bladder conditions met with in this group.

For years past urologists have known that after a tuberculous kidney has been removed the accompanying bladder lesion will usually heal within a few months; in a few cases, however, it persists, with serious bladder symptoms, and defies our curative efforts by the usual methods of irrigations, instillations, and local applications.

This persistent lesion is usually found in the vertex of the bladder, and often appears to be quite superficial and innocent, as compared with the far more extensive lesions that may have been present before the nephrectomy. The urine may be quite normal or show only an occasional erythrocyte or leucocyte. In brief, the evidence suggests strongly that in this residual lesion we are dealing with an interstitial cystitis or elusive ulcer rather than with a tuberculous ulceration.

In three cases I have removed these ulcers by operation and have failed to find any evidence of tuberculosis in the excised tissues. Conforming with our experience with elusive ulcer, there may be only one tiny apparently superficial but extremely painful lesion, or several of these small lesions, or one or more large congestion areas may be found in any portion of the bladder. Again one sometimes sees a widespread, dull, red area, resembling parchment, a portion of which may be covered by a dead white area of thickened epithelium quite devoid of vessels, the condition known as leucoplakia vesicae.

Keyes (personal communication) has given considerable study to such conditions as they persist after nephrectomy for tuberculosis, and has come to the conclusion that they should be treated just as one treats the elusive ulcer.

My experience with the frequent association of bilateral ureteral stricture and elusive ulcer of the bladder,[4] leads me to believe that most of these extremely persistent and painful lesions are of the elusive ulcer type (some of them possibly having been present before the onset of the renal tuberculosis), and that they should be treated as such, including careful attention to any distant focus of infection (see Case B).

CASE C.—Fig. 3 shows the right kidney, the urine from which was always negative for pathologic elements until in February, 1932, two years and four months after her left nephrectomy, a guinea pig inoculated with urine from the right kidney died six weeks later of tuberculosis.

M. S., aged fifteen, admitted to the Church Home and Infirmary, October 7, 1929, complaining of pain in the left flank region since her eleventh year. During these five years there had been spells of bladder frequency, but she was often free from urinary distress. Menstruation began about two years ago and was regular for about one year; there was then amenorrhea for six months, after which the periods occurred regularly from March until June this year. There has now been amenorrhea for the past four months.

The patient is a large-framed, emaciated girl. There have never been unusual chest symptoms. There was a suspicious area beneath the angle of the right scapula, and an x-ray film showed evidence of bilateral pulmonary disease. Heart sounds normal, about 100 per minute, temperature reached normal daily, but rose to a peak of from 100° to 103° F. daily during the seventeen days of observation before operation. Blood pressure 100/70. Hb. 68 per cent. R.B.C. 3,910,000. W.B.C. 13,700. Two-hour intramuscular phenolsulphonephthalein 45 per cent. The urine contained a heavy sediment representing half its volume and composed chiefly of pus cells, with many erythrocytes, a large quantity of albumin. Special stains on three occasions were negative for tubercle bacilli, and a guinea pig inoculated with urine from the left kidney failed to show any positive evidence of tuberculosis.

On palpation the left flank contained a mass, apparently the left kidney, reaching about 3 cm. below the umbilical line. We estimated this mass as being about 4 times the size of a normal kidney. The right kidney could be palpated over its lower third and seemed slightly enlarged as if from compensatory hypertrophy. No tenderness over right kidney nor over the right ureter at the pelvic brim. The left ureter in the region of the pelvic brim was tender. Pelvic examination was not made until anesthesia for operation, when the left ureter could be traced from the bladder almost to the pelvic brim as a thickened mass larger than a lead pencil. The right ureter could be traced for about 4 cm. beyond the bladder as a thickened cord the size of a slate pencil.

The bladder, when filled to discomfort, was catheterized and 110 c.c. were obtained. Cystoscopy revealed almost universal ulceration of the bladder. The mucosa of the base and trigonal region was so red and edematous that the ureteral orifices could be found only by probing with the metal searcher. Neither side could be catheterized. After a week of daily irrigations the bladder had improved somewhat. The left ureteral orifice was seen to be secreting a thick purulent material. The left side was catheterized and the urine was so purulent that it ran very slowly through the No. 8 catheter. Urograms showed all the lobules deeply excavated. In spite of the failure to find tubercle bacilli, the evidences of lung involvement, and of a

practically destroyed left kidney, with a negative culture from the purulent urine, were such as to prompt us to do a left nephrectomy. The fact that a catheter would not enter the right ureter, together with the findings on palpation during anesthesia, made us suspect that the right kidney might also be involved but its two-hour phenol-sulphonephthalein output of 45 per cent showed that it was capable of sustaining fair health, and we felt confident of improving its working capacity by later ureteral dilatation.

Left nephrectomy October 24, 1929, removing a kidney weighing 2.75 pounds, 1026 gm., or about 7 times the normal. The temperature chart for twenty-eight days until the patient's dismissal showed an elevation to 99° F. on two occasions. At our request the patient returned in February, 1930, four months after operation. She weighed 123 pounds, a gain of 33 pounds. The bladder had improved markedly in appearance, there being many normal-looking areas. The right ureter was entered with much difficulty due to dense infiltration in the lower ureter. The kidney urine was normal and negative for tubercle bacilli on slide stains and a guinea pig test. The following summary gives some idea of the progress in the more than two years after the left nephrectomy.

	OCT. 1929	FEB. 1930	FEB. 1931	MAR. 1931	JAN. 1932	FEB. 1932
Weight, pounds	90	123	150	153		
Blood pressure	100/70	126/90			122/78	
Bladder capacity in c.c.	110	260	270	330		
Right kidney capacity in c.c.		30	28		24	
Two-hour phenolsulphonephthalein per cent	45	51			55	60

In September, 1930, the patient had several hemorrhages from the lungs over a period of four days, this being the only active clinical sign of pulmonary disease she has had.

As before stated, there had been 3 stained slide examinations before operation with negative results. Two of these (October 8 and 14) were from the bladder urine and one (October 14) from the left kidney urine. A guinea pig inoculated with the left kidney urine on October 14 was autopsied on November 22, and showed a suppurating gland in the groin, but no other evidence of tuberculosis. A smear from the suppurating gland and stained sections of the gland were negative for tubercle bacilli.

After the operation stained slides were made from the bladder urine on February 7, 1930, and from the right kidney urine on February 7 and February 17, 1930, all being negative. Guinea pigs were inoculated after operation with the bladder urine on February 7, 1930, and on February 2, 1931. The latter animal was autopsied March 16, 1931, and was positive for tuberculosis. Urine from the right kidney was inoculated February 17, 1931, and February 24, 1932. The latter animal was autopsied April 7, 1932, and was tuberculous. During the two years the urine from the right kidney was examined on 6 occasions, but leucocytes were never found. Serious bladder symptoms had always been surprisingly absent even on the first visit when a normal area of mucosa could not be seen, and the capacity was only 110 c.c. On the last visit in February, 1932, the patient reported voiding only once or twice at night and at three- to four-hour intervals in the day. The mucosa still showed general congestion with many areas of brilliant redness. Some of these areas were partially covered by a fibrinous-like coating, but this could not be re-

Fig. 3.—Urogram April 22, 1931, 28 c.c. NaI, catheter out. Note well filled lower half of pelvis with clean-cut outlines. Other urograms of entire kidney show similar sharp outlines. Partially filled ureter showing convolutions. Narrow lumen in bladder wall region. Note the unusual picture of a cone-shaped spurt of NaI from the ureteral orifice.

Fig. 4.—Case 1. Plain plate showing tip of x-ray catheter curved up over a stone the size of a navy bean located beside the third lumbar interspace. Note that the patient has six lumbar vertebrae, and that there is fusion of the third and fourth. The history suggests that the patient had an active invasion of the spine when at school at fifteen years of age, the symptoms subsiding completely after five months of rest.

moved by brushing it with a dry cotton pledget, and I interpreted this as a leuco-plakic process of healing.

THERAPEUTICS

What therapeutic evidence have we that the restoration of better urinary drainage by thorough dilatation of ureteral stricture may favorably influence the progress of renal tuberculosis?

Since the development of this new conception of the etiology of renal tuberculosis, we have had the opportunity to make use of it therapeutically in only 6 cases. The elapsed time has been too short and the number of cases far too few to justify conclusions of any kind, but our

Fig. 5.—Case 1. Urogram after the stone had passed, showing pelvis of 50 c.c. capacity, stricture area in the broad ligament region with moderate dilatation of the pelvic ureter, and wide dilatation of the abdominal ureter which is incompletely filled. The original film shows plainly a narrow area opposite the fourth lumbar from which the stone was dislodged after several dilatations.

experiences to date suggest that further critical studies should be made in this important field.

CASE 1.—(Figs. 4 and 5.) In the case of a patient thirty years of age, who had lost one tuberculous kidney by nephrectomy, we were forced into this drainage treatment as the only method available for helping the remaining tuberculous kidney. She had a stricture in the broad ligament region and a high stricture containing a stone at a point opposite the third lumbar vertebra. We were able to dilate both these strictures and get a spontaneous passage of the ureteral stone.

On admission this patient's hemoglobin was 65 per cent, the intravenous phenol-sulphonephthalein test showed, first hour, 110 c.c. 8 per cent, second hour, 550 c.c. 42 per cent, and the nonprotein nitrogen was 54 mg. per cent. During four months of treatment in which the ureteral dilatations were carried up to 5.6 mm. (17 Fr.), the patient had occasional attacks of discomfort in the right flank, accompanied
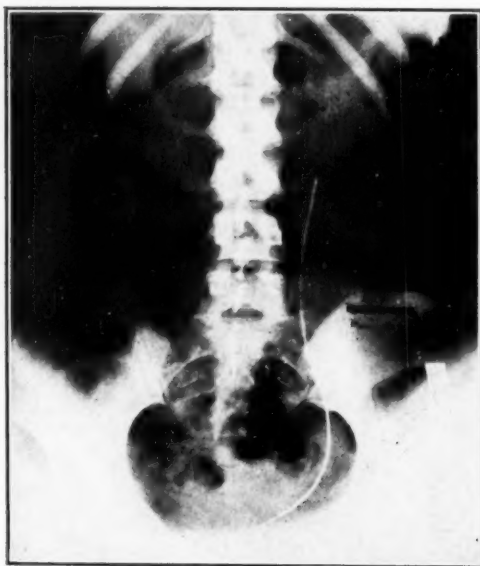
Fig. 6.—Case 2. At the first investigation the catheter tip was obstructed in passing through the broad ligament region, and this film shows the tip permanently stopped at about the level of the lower pole of the left kidney. Two tiny calcareous particles appear in the upper portion of the kidney.
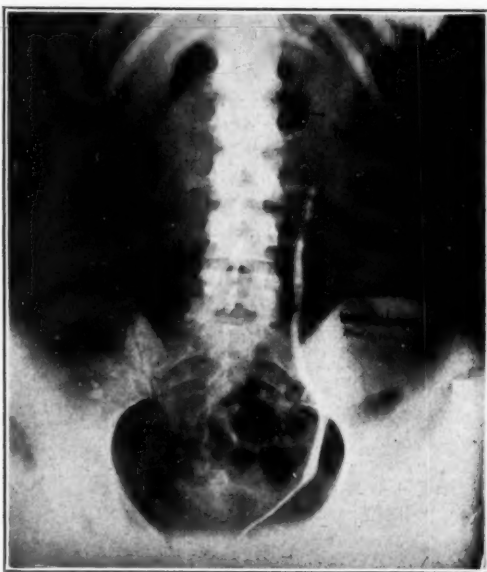
Fig. 7.—Case 2. The catheter has been withdrawn until its bulb, 10 cm. back from the tip, is hanging in the broad ligament region about 3 cm. above the bladder. Note the slight dilatation of the ureter from this point to the kidney, except for two areas of filling defect near the kidney, and that no urogram solution gets through into the pelvis. In the original film the filling defects in the upper ureter show an irregular feathery or nodular outline suggesting neoplasm or tuberculosis.

by headache and nausea, showing that her stricture areas still narrowed down at times and interfered with drainage, and that her tenure of life was not at all promising. These attacks were particularly prone to occur with the menstrual periods. Her general health and ability to take moderate exercise improved, but she died thirteen months after she left our care.

CASE 2.—(Figs. 6, 7 and 8.) In a second case with bilateral renal involvement we probably saw the patient too late to give the drainage method a fair trial. It was evident that both kidneys were badly diseased, but the showing of a normal blood chemistry and a two-hour intravenous phenolsulphonephthalein output of first hour 45 per cent and second hour 15 per cent, and a half-hour differential test showing,

	APPEARANCE TIME	AMOUNT	PER CENT
Left kidney (catheter)	6 minutes	135 c.c.	30
Right kidney (bladder)	15 minutes	44 c.c.	2
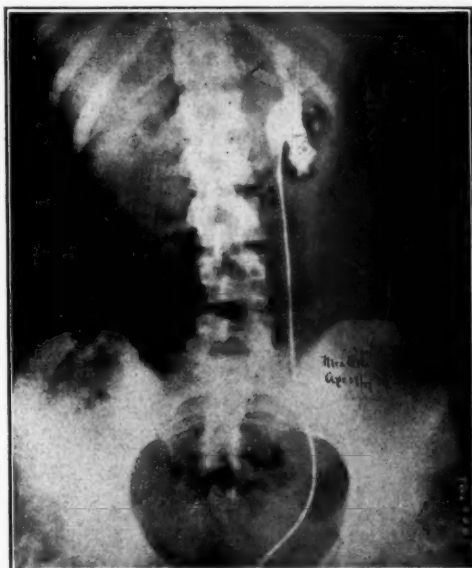
Fig. 8.—Case 2.   Taken one month after Figs. 6 and 7, showing that the tip of a No. 7 catheter with an 11 Fr. bulb placed near the tip had gone well over into the kidney.   The kidney held 10 c.c. of urogram solution.   The urogram suggests slight hydronephrosis with slight reflux of solution down the ureter for a distance of 4 cm. (Compare upper ureter in Fig. 7.)   Deformity of all calices, the uppermost calyx being clubbed and its neck almost cut off, suggesting an abscess cavity in the upper pole.   Two others of the upper calices almost obliterated.   Two middle calices showing tiny cups and thin necks almost obliterated.   The lower calices dilated and merging broadly with the pelvis.   On withdrawal of the catheter the small bulb near the tip had a rather firm hang near the kidney in two areas, at about 26 cm. and 24 cm. from the outside and in a third area near the bladder (see Fig. 7).

We felt that improved ureteral drainage offered the only possible hope for improvement.

After inadequate ureteral dilatation had been established in the spring of 1927, the patient went north for the summer vacation. In the fall her husband wrote that she had gained 13 pounds in weight and that her general health seemed improved. They had decided to avoid the long trips to Baltimore and to have further treatment by a home surgeon in New York City. After the usual investigation and a confirmation of the bilateral tuberculosis, it was decided that her general and renal conditions did not justify further active interference and the patient died in January, 1928.

Fig. 9.—Case 3.   Tuberculous pyonephrosis right kidney.   Note the stricture area about 3 cm. above the bladder and the large ureter and kidney holding 50 c.c.   Note apparent obliteration of the uppermost calyx and slight filling defect of the lower calyx.

Fig. 10.—Case 3.   Left kidney pelvis and calices slightly smaller than normal, holding 5 c.c.   The bulb repeatedly demonstrated 5 stricture areas in beadlike sequence, the highest being 16 cm. above the external urethral orifice.   Note the upper filling defect opposite the lumbosacral joint, and three filling defects in the pelvic ureter.

CASE 3.—(Figs. 9 and 10.) In a third case our preliminary investigations made us quite certain that we were dealing with a tuberculosis of the right kidney, but the miraculous improvement in the local and general conditions of the patient after a few ureteral dilatations forced us to question our original diagnosis. Miss B., aged twenty-one years, was referred by Dr. Julius Friedenwald in March, 1926. There had been moderate attacks of pain in the right upper flank region on five occasions in the previous two years. The patient's mother had died of tuberculosis, and the patient was of the tall frail type, but quite athletic in her pursuits.

Physical examination and x-ray of the thorax were negative. The patient had not been conscious of her side between attacks and there had never been urinary frequency. The bladder urine showed about one-fifth of the volume as a heavy purulent deposit, and a trace of albumin, but was negative to culture. Palpation revealed slight tenderness over the lower pole of the right kidney and great tenderness over both ureters in the broad ligament regions, the left seemingly showing more tenderness than the right. On cystoscopy the bladder everywhere appeared to be normal except in the trigonal area, which was deeply red and congested, and the right mons ureteris was "puffy and edematous, suggesting a tuberculous condition."

Further investigation revealed bilateral ureteral stricture with a 50 c.c. pyonephrotic kidney on the right, the left kidney pelvis being smaller than normal, holding only 5 c.c., and yielding normal urine. The half-hour intravenous phenol-sulphonephthalein test, after both sides had been well dilated, showed an output of 20 per cent on the right and 45 per cent on the left.

Under dilatations the patient gained 20 pounds in weight in the first two months and at the end of four months the following note was made on the urinalysis: "Urine catheterized from the bladder, after standing six hours, looks like clear water, shows no visible precipitate; pipetted and centrifuged. A slide preparation shows 1 to 4 leucocytes in a high-power field, a few epithelial cells, no erythrocytes, no casts; there was no albumin."

Fifteen months later the patient again developed symptoms, and the bladder urine was found to contain about half as much pus by volume as on the first investigation. I was unable to pass even the finest whalebone filiform through the stricture area in the right broad ligament region. For the first time we demonstrated tubercle bacilli by guinea pig test, and right nephrectomy was done two years after the first consultation.

This case illustrates the difficulties sometimes encountered in making a positive diagnosis of tuberculosis of the urinary tract. During the two years of observation and treatment this patient had been in two hospitals on ten different visits, and because of the original urinary and cystoscopic findings I had suggested the likelihood of finding tubercle bacilli. In each of her admissions at least one and sometimes several examinations were made of the urine from the bladder or from the right kidney. Either one or two guinea pigs were inoculated on four different occasions and the sixth was the first to die of tuberculosis.

One of the strongest arguments against the right kidney being tuberculous was the prompt manner in which the urine cleared up when we first established good drainage. Before the experience with this case I held the view that if a pyonephrosis or an infected hydronephrosis does not promptly clear up with the establishment of good ureteral drainage, we should exert every effort to demonstrate tubercle bacilli, even though the urine on culture yields a pyogenic organism, but here we have

a case in which drainage resulted in such rapid clearing of the urine that we were almost diverted from any further search for tuberculosis.

The two following cases, illustrated by Figs. 11 to 14, seemed to offer a fair test for the drainage method of treatment, but one patient has had the tuberculous kidney removed and the other has been advised to follow this course. Each presented bilateral ureteral stricture, and unilateral renal tuberculosis with approximately equal and normal bilateral functional tests. Each of them showed gain in weight and improvement in general health as an early result of the bilateral drainage.*

The following case represents an apparent cure of a bilateral renal tuberculosis, following no other measures than the establishment of good ureteral drainage. The patient had a definite history of right renal attacks for five years; with one attack on the left side, and the passage of a ureteral stone, two years previously. These phenomena are not uncommon in cases of simple ureteral stricture. The x-rays revealed advanced bilateral hydronephrosis, also a common sequel of stricture; but the flat film showed multiple deposits in the calices which led to the discovery of tubercle bacilli in abundance in spite of an almost perfectly normal urinalysis.

CASE 6.—(Figs. 15, 16, and 17.) Mrs. M. L., aged thirty-five, para iii, first admitted to the Johns Hopkins Medical Service October 23, 1919, because of a severe attack of pain in the right upper quadrant and intense jaundice. Six attacks of similar pain without jaundice in the previous eight months. On admission she was also suffering with a marked Vincent's angina and a right parotitis. Tonsillitis attacks over a period of many years, and diphtheria in 1909. Two dental abscesses four years previously.

After subsidence of the acute condition about the mouth, parotid and gall bladder regions the patient was transferred to the surgical service on December 5, and on December 10 a diseased appendix and gall bladder were removed. Gall stones were not found in the bladder or ducts, but the gall bladder had a deep hour-glass constriction in its midportion and dense adhesions to the duodenum. Drainage to the common duct was instituted by means of a small rubber tube sutured into the cystic duct. The patient made a rapid recovery and first entered the gynecologic dispensary about six and a half years later, or in June, 1926. About one year after the operation she began having attacks characterized by an uneasy feeling in the mid-epigastrium which disappeared after massage followed by belching. Later severe attacks began with pain in the right posterior flank region, working forward into the epigastrium, and ending in marked nausea and vomiting. These attacks formerly occurred at intervals of about five or six months but in the past year they had come at about monthly intervals and there had been 3 attacks in the past month. Hypodermics of morphine were frequently necessary in these attacks. The urinalysis was negative except for a few erythrocytes and a large amount of amorphous débris.

About two years before admission she had had a similar severe attack on the left side and a small stone had been passed. She entered a neighboring hospital where catheters were passed and x-rays taken, and she was more comfortable for about six months. At the present time she has no marked bladder symptoms, but she

---

*To economize space the detailed histories of Cases 4 and 5, Figs. 11 to 14, are omitted in the JOURNAL but will appear in the reprints to be furnished by the author on request from those especially interested in this subject.

voids about twice at night, and at two-hour intervals in the day. With the attacks she often voids at hourly intervals.

Cystoscopy revealed an apparently normal bladder except for numerous glistening vesicles scattered over the posterior wall, and a red edematous condition of the

Fig. 15.—Case 6. Urogram, right side, 50 c.c. NaI. Deformity of calices, with suggestion of filling defect in middle and lower calices. Calcareous deposits outlining calices of left kidney. Phleboliths or calcified glands in both broad ligament regions.
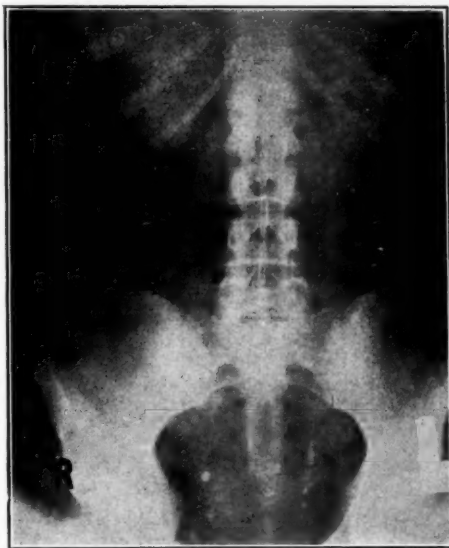
Fig. 16.—Case 6. Flat film, taken five years after Fig. 15, showing two stones of irregular outline in the lower end of the left ureter.

trigonum and around the ureteral orifices. The latter suggested tuberculosis, but the absence of pus after a history of attacks over a five-year period was strongly against such a diagnosis. In nearly all later examinations we were able to demonstrate

an occasional pus cell in the centrifuged urine from the bladder and from either kidney. Further investigations in the succeeding weeks revealed bilateral ureteral stricture and bilateral hydronephrosis, the right kidney holding 50 c.c. (Fig. 15) and the left 26 c.c.

The patient was a large-framed woman, weighing 150 pounds. General physical examination was negative except for enlarged, angry-looking tonsils, a suspicious dental condition and tenderness on palpation of the right kidney and over both ureters at the pelvic brim and broad ligament regions. A hard nodule was palpated in the right broad ligament region and interpreted as being a phlebolith.

The plain x-rays revealed numerous tiny shadows in the region of practically all the calices. With this evidence a search was made and tubercle bacilli were found in abundance in the catheterized bladder urine. Guinea pigs inoculated on September

Fig. 17.—Case 6. The No. 9 whistle-tip x-ray catheter has displaced both ureteral stones up into the kidney pelvis.

14 from the bladder and left kidney urines, on September 23 from the right kidney urine, and on September 26 from the left kidney all died from tuberculosis.

The ureteral dilatations were carried up to a 6 mm. (18 Fr.) dilatation and the patient rapidly improved in general health, her only complaint being that she was ''getting too fat.'' Her weight increased from 150 to 168 pounds in the first ten months of treatment, and to 178 pounds in the next year. In January, 1927, we found that an irregular angular stone had lodged in the right ureter. This was probably caused by the coalescence of smaller calculi which had become freed from the deposits in the calices. Being irregular in outline it was difficult to dislodge from the stricture area in the right broad ligament region, but its irregularity probably also allowed free drainage of urine, for the patient was not inconvenienced by it. This stone passed spontaneously in March, 1927. Negative guinea pig inoculations were made as follows: R. kidney xii, 10, 1927; ii. 14, 1928; ii, 14, 1929; iii, 5, 1929; L. kidney xii, 29, 1927; iv, 5, 1928; ii, 29, 1929; vi, 26, 1929. Many stains were made from the bladder and kidney urines during the three years from June, 1926, to June, 1929, the specimens often being centrifuged for a long period and examined

most carefully, and after the first six months of her treatment tubercle bacilli could not be demonstrated.

In spite of our urging that the patient report at six-month intervals she was so well that we did not see her from June, 1929, until April 2, 1931. At that time she returned because of a dull pain in the left side. Investigation revealed two stones in the left ureter, one about 2 cm. and the other 1 cm. long (Fig. 16). These stones appeared irregular in outline, and after our experience with the prolonged difficulties of dislodging the conglomerate stone from the right ureter in 1927, we decided to remove these left ureteral stones by operation. These stones were migratory and could be displaced upward into the kidney by the whistle-tip No. 9 x-ray catheter (Fig. 17), but in spite of a dilatation up to a 4.6 mm. (14 Fr.) the stricture areas would not allow the stones to pass. Unlike the one on the right side, these stones caused enough blockage of the ureter to bring on renal pain and fever, the chief factor in the decision for operation. This was done June 11 through a left McBurney extraperitoneal incision, and we had considerable difficulty in dragging all the stone material up from the broad ligament region. Like the former stone on the right side, these stones on the left were apparently conglomerates, made up of fused particles coming down from the calices. After their removal, dilating bougies up to a 15 Fr. were passed through the stricture in the broad ligament region, and the ureter was left open for free drainage in case the trauma of the operation should result in edema and temporary closure of the stricture area. In one week the urinary drainage had ceased and the cigarette drains down to the region of the ureter were removed. Before the operation guinea pigs were inoculated from the urine from each kidney and both were negative for tuberculosis. Slides were stained on numerous occasions from specimens from the bladder and both kidneys, and all were negative.

The patient was discharged in good condition at the end of four weeks. Three weeks later, or on July 31, 1931, she was brought to the hospital at night in a moribund condition after an apparent history of intestinal obstruction of one week's duration. She was taken directly to the operating room in the hope that intravenous fluids might place her in condition for an exploratory incision under local anesthesia. The abdomen was greatly distended and there was an indefinite mass in the right upper quadrant. While taking the intravenous glucose solution and before an incision could be made the patient died.

Our resident gained permission to make an exploratory incision which revealed 2 or 3 feet of black jejunum, the infarct being due to a volvulus of the mesentery. Unfortunately permission to remove the kidneys was refused and a unique opportunity was missed to ascertain whether after five years of good drainage there had been actual healing of the tuberculous process.

You will note in the program synopsis of my paper that I proposed to report one case of unilateral renal tuberculosis as cured. Since digging into the records of this patient I am disappointed in having to drop her from our tuberculosis list. These records furnish such a striking example of the care one must use in arriving at a diagnosis of renal tuberculosis, and show so well the rôle of ureteral stricture in causing many of our common urinary tract complaints that a brief summary of the facts are pertinent.

In 1927 one of our resident gynecologists showed me the urogram (Fig. 18) of a patient he had been treating for supposed right renal tuberculosis and gave me from memory the following data. Tubercle

bacilli had been found in abundance in the urines from the bladder and right kidney and guinea pigs inoculated from these sources had died of tuberculosis.

After six months dispensary treatment of bilateral ureteral stricture the patient was symptom-free, the urine was normal, careful slide and guinea pig examinations for tubercle bacilli were negative, and the resident considered the case as one of recovery from renal tuberculosis. The facts seem to be as follows:

CASE 7.—Mrs. E. H., aged twenty-seven, para iv, was admitted to the gynecologic service July 15, 1926, complaining chiefly of pain in the right flank, hematuria, and acute arthritis of the metacarpophalangeal joint of the right index finger. Seven years previously in the third month of her third pregnancy the patient had had a

Fig. 18.—Case 7. Right urogram of patient with bilateral ureteral stricture erroneously diagnosed as right renal tuberculosis.

spell of great urgency and frequency of voiding, with hematuria. This had soon cleared spontaneously and there had been no further trouble in that or the subsequent pregnancy. Since that first attack there had been intermittent spells of frequency but no bleeding until the present illness. For the past six months the patient had grown progressively weaker. Has had nervous and crying spells. At times sudden slight fever and in the past few weeks, night sweats. Spells of dry cough without hemoptysis. In the last few months occasional pains in the upper chest, considerable headache. In 1917 "pneumonia and influenza." Occasional mild sore throat since. Two months ago began to have intermittent attacks of sharp pain in the right flank region, and these have been more severe and persistent since an attack of tonsillitis two weeks ago. For the past week there has been much urgency and urinary frequency, and the passage of bloody urine. The acute arthritis of the right hand began at about the same time, together with fever. The catheterized bladder specimen showed many erythrocytes and leucocytes and a culture of bacillus

coli. Because of the history suggesting an early pulmonary tuberculosis, and a more recent tonsillitis followed by possible acute hematogenous nephritis, and because the patient's chief complaints on admission were centered on the acute and painful arthritis, she was referred for study to the medical service.

Evidences of chest tuberculosis were absent. Blood cultures and the Wassermann test were negative. A Streptococcus hemolyticus was recovered from the right tonsil. The urine was carefully centrifuged on four successive days, and on three of these acid-fast bacilli were found. The note on the last examination states, "A voided specimen was then treated by the method of Petroff and after 50 per cent alcoholic dilution was centrifuged at high speed for two hours. Sediment then stained by the method of Ziehl-Nielsen and a clump of three acid-alcohol-fast bacilli were seen. These were examined by several members of the medical house staff, who agree that morphologically they are Koch's bacilli."

After nineteen days in the hospital the patient's arthritis had subsided, her temperature was normal, and the urine was free from pus and blood. She was then referred back to the gynecologic service for further investigation for a possible renal tuberculosis. Bilateral ureteral stricture was found, the urine from each kidney being normal. Tubercle bacilli were not found on stained slides after the patient's transfer to the gynecologic side.

During July, August, and September guinea pigs were inoculated as follows: four times from the bladder urine, and four times from the kidney urines, twice from each side. Evidences of tuberculosis were not found in any of these eight pigs. One naturally wonders on what basis the case was reported to me as one of tuberculosis. On investigation of the medical records I find that four examinations were made of the bladder urine, one of a catheterized specimen, in which tubercle bacilli were not found, and three on voided specimens, in all of which acid-fast bacilli were found. The patient was found to have an inflammation of Skene's glands, the pus from this source showing intracellular diplococci. These facts seem to point to the one conclusion that the acid-fast organisms originally identified as tubercle bacilli should have been called smegma bacilli. As further evidence that this patient's urinary tract troubles originated from a ureteral stricture condition, I found on the recent review of her records that she remained well nearly four years, and then returned in 1930 with many of her old symptoms such as malaise, extreme nervousness, night sweats, pain in the right flank, fever, and frequency of voiding. After a few dilatations these symptoms ceased.

This patient undoubtedly represents one of that great group seen in urology in whom the pathologic conditions in the kidney and general ill health are largely dependent on inadequate renal drainage secondary to ureteral stricture. It would be useless to speculate on what proportion of nephrectomies for supposed tuberculosis belong in this group. Fortunately, the number grows rapidly less since surgeons are now making use of the diagnostic and therapeutic methods made possible by a knowledge of ureteral stricture.

Is it wise to suggest the possibility of any other method of dealing with renal tuberculosis than by nephrectomy, which we have found so promptly effectual in such a large proportion of our cases?

It is perhaps fortunate that this first report on the drainage method makes such a poor showing in actual results that no one should be carried away by an enthusiasm which might lead to such an indiscriminate use of the method as to work harm to the patient.

Our present diagnostic methods in urology, including the microscopic study of the separate urines from each kidney, the differential functional tests, the x-ray studies, and the bulb studies of the ureteral condition, are now so perfected that we can arrive at a fairly accurate estimate of the condition of each kidney. For the present time at least, and until we have had far greater experience, this drainage method should not be tried except in those patients whose renal lesion seems to be of of moderate extent and the affected kidney of good working capacity.

Curiously enough, and as a striking example of the futility of dogmatic attitudes in dealing with renal tuberculosis, the very patients on whom we obtained the most striking results in the above list of six cases treated by drainage, were two (Cases 3 and 6) in whom our diagnostic yardsticks indicated that we were dealing with a widespread and advanced renal involvement; whereas Cases 4 and 5, apparently showing slight involvement, were the most disappointing in ultimate results.

In Cases 4 and 5 the patients came from a midwestern state and could be treated only at intervals of about six months. In the future I would undertake the drainage methods only in patients who live near enough to be seen conveniently at any time.

We know that tuberculosis heals in various portions of the body, and theoretically the kidney, with its rich circulation and ideal methods of irrigation, should offer an unusual area for spontaneous healing. If, as our experience seems to indicate, ureteral stricture is the chief factor of interference with the natural irrigation properties of the kidney, we may look for healing in a certain number of cases if we can restore good drainage. We are certain that in dealing with chronic pyogenic infections of the kidney there has been no other healing method to compare with that of establishing good drainage through dilatation of the ureteral strictures. In renal tuberculosis any area of ureteral obstruction may be the site of tuberculosis and as such it offers a more serious problem in treatment than simple stricture. We know that bladder tuberculosis often heals, why should ureteral tuberculosis not do so?

This report is justified if the general adoption of bilateral ureteral dilatation is limited to patients who have bilateral renal tuberculosis. It is generally agreed that surgery is contraindicated in such cases except when one kidney is practically destroyed and is the source of severe toxic symptoms, while the other kidney is doing fairly good work. In such cases bilateral ureteral drainage, if feasible, before operation, will probably improve the patient's condition and render operation less dangerous, and the later careful attention to ureteral drainage on the remaining side should do much to reduce discomfort and prolong life. A friend, who had undoubted bilateral renal tuberculosis and had had the more damaged kidney removed, lived a most active and highly useful life for eighteen years after the nephrectomy. We have seen several bilateral cases in which, without drainage treatment, the patients have surprised

us by their comparative activity and length of life, and in the future we shall undoubtedly be able to alleviate such conditions.

Case 6 affords a striking example of what may be accomplished in a patient showing every evidence of widespread involvement of both kidneys. In the early films nearly every calyx area was spotted with calcareous deposits presumably indicating universal ulceration. Five years later, in spite of the acute renal inflammation caused by partial block of ureteral stones, we were unable to demonstrate tubercle bacilli by stain or guinea pig inoculation.

Another group in which the method of drainage cannot be criticized is illustrated by Case 1, and includes those patients who have lost one kidney from any cause and present with a tuberculous condition of the solitary kidney.

In some patients of advanced age, especially if there be other contra-indications to operation, this method of drainage may prove of distinct palliative value. This would apply particularly to those who are fortunate enough to have escaped serious bladder symptoms. Case A illustrates that, with bladder symptoms of severe grade, the dilatation of the non-tuberculous side may greatly alleviate these symptoms, even before the removal of the tuberculous kidney. In several previous publications I have shown that simple ureteral stricture is one of the most common causes of serious bladder symptoms, even inducing complete incontinence of urine; and one of the most satisfactory discoveries in the study of cases with elusive ulcer of the bladder has been that in a considerable proportion of those who have both ureteral stricture and elusive ulcer, the thorough dilatation of the ureters results in such reduction of the bladder symptoms that we are not called upon to treat the bladder lesion.

In certain cases in which tuberculosis is strongly suspected, we are justified in continuing the drainage treatment until we can prove the presence of tuberculosis, providing the patients are answering favorably to the treatment as in Case 3.

In the apparently early unilateral cases we have probably lost no ground by the delay of a few months in doing a nephrectomy, should this become necessary because of a progression rather than a regression of the tuberculous process.

The strongest argument against the method is the danger of carrying infection to the nontuberculous side in making repeated dilatations of the simple ureteral stricture on this side. In my first paper on renal tuberculosis twenty-eight years ago, I strongly condemned the passage of a plain catheter to the supposedly healthy side even for the purpose of more accurate diagnosis, and many writers since have emphasized this danger. I know of no one who has seen definite evidence of this transplanting of the disease, but the theoretical dangers seem so great that we should use the utmost precaution in dealing with the nontuberculous side. It may be fairly questioned whether tubercu-

losis was carried from a diseased bladder to the kidney in our Case C. We failed to catheterize the good side in the one attempt before operation. Tuberculosis was not proved until the immense left kidney was removed. Four months later we began dilatation of the right ureter, and in two years of intermittent treatments leucocytes were never found in the kidney specimen. A guinea pig inoculated with bladder urine one year and four months after operation died of tuberculosis. A guinea pig inoculated with the right kidney urine two years and four months after operation died of tuberculosis. Was this infection carried to the kidney from a tuberculous bladder, or were both of these pigs killed with tubercle bacilli which temporarily were being secreted through the blood stream from the known lesion in the lung?

If in the individual case evidences of stricture are wanting on the better side, no further treatment is indicated. If stricture and evidence of stasis are present on the nontuberculous side, our present knowledge leads us to believe that we must at least weigh the danger of blood stream infection of that side, because of the stasis, against the danger of even careful manipulations through the bladder in the effort to dilate the stricture, relieve the stasis, and restore a more normal renal circulation. While thus relieving the local situation, we may be adding tremendously to the patient's general powers of resistance by incidentally relieving headache, gastrointestinal and bladder symptoms, all of which may be partially due to the stasis and absorption of toxic products incident to the stricture on the supposedly normal side. The gain in weight and general well-being was a striking phenomenon in the last four of the above six verified cases, or in those who had a fair trial of the drainage method.

CONCLUSION

I would urge that, in the absence of contraindications to operation, early nephrectomy is the only treatment in those cases in which preliminary studies reveal a badly involved tuberculous kidney on one side only. This was done in 6 of our 12 cases and all these women are living in apparently good health, but I attribute this good condition in part to the treatment of establishing good drainage for the remaining kidney, as illustrated by our Cases A, B, and C.

REFERENCES

(1) Johns Hopkins Hosp. Bull. **15**: 1, 1904. (2) New York M. J. **104**: 5, 1916. (3) The Etiology of Ureteral Calculus, Surg. Gynec. Obst. **27**: 252, 1918. (4) *Hunner:* J. Urol. **24**: No. 6, 1930.

THE DIAGNOSIS OF PERITUBAL ADHESIONS AND TUBAL STRICTURES BY UTEROTUBAL INSUFFLATION*

I. C. RUBIN, M.D., F.A.C.S., NEW YORK, N. Y.

STRICTURES of the fallopian tubes may be slight or almost occlusive. In any case their presence is of importance as a cause of sterility. They may be due to partial agglutination of the folds of the tubal mucosa or to adhesions and angulations with so little thickening, as not to be palpable. Firmer adhesions and distortions which are not associated with distention of the tube may also escape detection by bimanual examination. It is with these nonpalpable lesions that the present paper is concerned.

As bougies are out of the question unless a laparotomy is performed, some other method must be sought which will enable us to diagnose such permeable strictures clinically. Such a diagnosis is possible with the use of uterotubal insufflation combined with the kymograph.

An apparatus has been described which supplies and regulates the flow of carbon dioxide gas, combined with a syphonmeter (volumeter), a manometer, and a kymograph upon which the pressures reached during the insufflation are recorded (Fig. 1).

It has been found that normal tubes not only allow the gas to pass through them freely under relatively low pressures but in addition oscillations are observed that have a rhythmic character (Fig. 2-a). These oscillations have been demonstrated to be due to rhythmic contractions of the fallopian tubes. They show only slight variations in frequency per minute in the postmenstrual interval when the test is most suitably carried out.

If the tubes are sealed, the pressure oscillations are absent. As a rule sealed tubes can tolerate a pressure of 200 mm. Hg which has been selected as the high limit of safety to which the tube may be subjected during the insufflation (Fig. 2-b). This is arbitrary but holds for most cases. If higher pressures are used and the gas is found to have entered the peritoneal cavity it indicates that we are dealing with very high grade strictures or that the closed tubes have ruptured. Spastic tubes may resist high pressures but when the spasm is overcome rhythmical contractions are the rule (Fig. 2-c).

High grade strictures have almost the same significance as complete closure of the tubes. In very rare exceptions, nature (with or without the aid of insufflation or lipiodol injection) may succeed in surmounting the difficulty and pregnancy may take place. Observers have recorded occurrences of this kind and I have met with a few instances.

Whether the stricture is relatively mild or extremely tight, the type of curve is more or less the same, higher pressures accompanying the tighter strictures. In normal tubes there is a sharp rise and fall in pressure with typical oscillations varying in depth between 15 to 30 or more
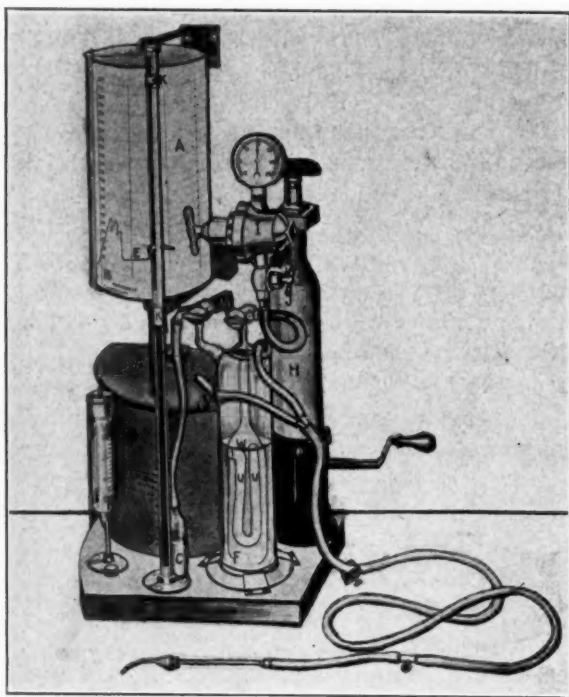
Fig. 1.—Apparatus for uterotubal insufflation. *A*, kymographic drum; *B*, the spring motor; *C*, mercury manometer with float (*D*), and ink writing pen (*E*); *F*, glass syphonmeter with two stopcocks (*G*) closed, to prevent the solution from spilling, when the apparatus is carried in the horizontal position in its case; *H*, carbon dioxide cylinder; *I*, pressure reducing valve with pressure gauge; *J*, needle valve for fine adjustment of the gas flow; *K*, safety (blow off) valve.

mm. Hg (Fig. 2-*a*). In the case of strictures the rise of pressure is more curved, the descent is more gradual and there is apt to be complete absence of typical oscillations. The absence of oscillations indicating loss of tubal contractions is constant in the high grade strictures where the initial pressure rise is well above 100 mm. Hg, most often between 150 and 200 mm. Hg. In the relatively mild strictures due to circumscrib-

ing adhesions there may be noted atypical oscillations which are very shallow and arrhythmic. When the tube is bound down lightly as by filmy adhesions which do not distort it, there may be the slightest variation from the normal. It may be mentioned in this connection that in prolonged amenorrhea tubal contractions may be absent.

If the tube is bound down by very firm adhesions on all sides so that its motions are impaired, the rhythmic contractions are not seen although the pressure levels may not exceed the normal.

There also appears to be a marked difference due to the location of the stricture, i. e., at the isthmus or the ampulla. Isthmic stenosis is more apt to block tubal peristalsis and interfere with rhythmic contractions to a greater degree than stenosis situated at the ampulla or the fimbria.
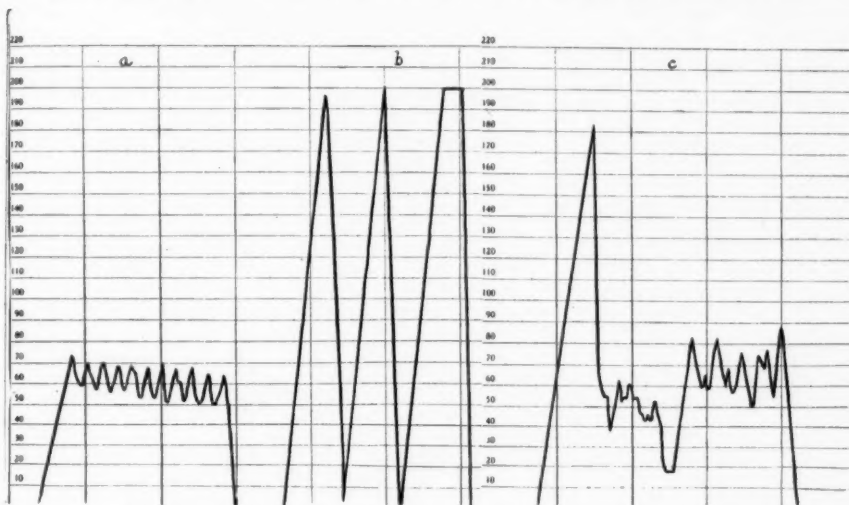
Fig. 2.—a, kymographic record of normal tubal patency; b, kymographic record of tubal nonpatency; c, kymographic record of uterotubal spasm.

Observations bearing upon these points were made by checking the insufflation findings by:

1. Laparotomy and clinical examination.

2. Findings after lipiodol injection.

3. Experiments upon surviving extirpated human uteri and tubes, and upon these organs removed from the sow.

1. LAPAROTOMY AND CLINICAL OBSERVATIONS

Opportunity was afforded to compare the insufflation findings with observations at laparotomy in 35 cases in which tubal stenosis and peritubal adhesions were found. In 16 cases insufflation was done before and after operation; in 10 cases before operation only; and in 9 cases insufflation was done for the first time after an operation. In the latter the operative data were available and could also be judged in relation to the insufflation curves. The results were uniformly corroborative in

the 26 cases in which insufflation preceded the laparotomy. In the remaining 9 cases the insufflation findings give an idea of the present status of the tubes following operation (Figs. 3 and 4).

In the presence of peritubal adhesions without constriction of the lumen, the pressure at which the curve was maintained was not ele-
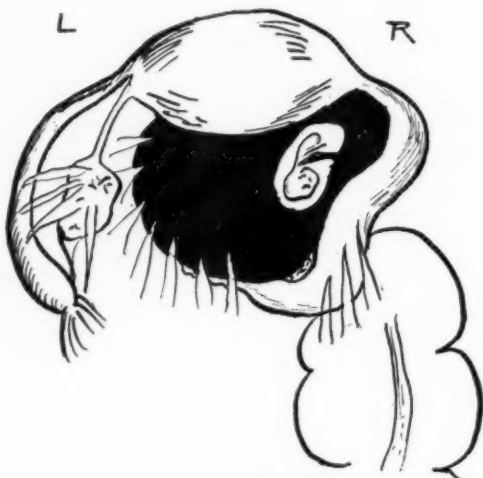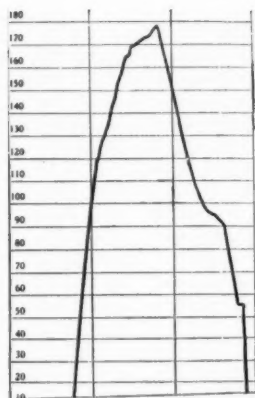
Fig. 3.   Fig. 4.

Fig. 3.—Insufflation of a residual stenosed tube after a tubal pregnancy. Operative findings June 20, 1929. Rupture of a tubal pregnancy in the ampullary portion of the right tube; the left tube was found embedded in a few filmy adhesions which were separated.

Fig. 4.—Postoperative insufflation of left tube November 1, 1929, of Fig. 3. Subphrenic pneumoperitoneum right side 1¼ inches in depth; left side one-fourth inch.
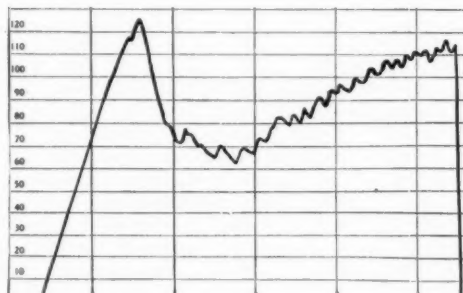
Fig. 5.—Adherent residual tube after a tubal pregnancy. Left tube was removed. The right adnexa was found adherent to the pelvic wall; adhesions were separated. Operation October 1, 1931. Graph of postoperative insufflation October 14, 1931. Positive subphrenic pneumoperitoneum; note shallow curves typical of adherent but patent tubes.

vated but the contractions were infrequent, irregular, shallow or entirely absent depending upon the degree of immobilization produced (Fig. 5).

In the presence of tubal stenosis, whether of extrinsic or intrinsic origin, the initial rise of pressure was as a rule well above 100 mm. Hg. Instead of dropping sharply and exhibiting oscillations, the curve produced was rounded and the descent gradual. When this form of curve

is produced it indicates that both tubes are mechanically impaired, because if one tube is normal the kymographic tracing assumes the normal pattern.

In judging the location of the stricture special attention was paid to the pain reaction experienced during the insufflation. Pain, as a rule, was not severe enough to cause spontaneous complaint on the part of the patient during the insufflation. On direct inquiry the patient is able to state where the pain is located and its manner of radiation.

Stricture may be located at the uterotubal junction, at the isthmus, and at points along the ampulla and fimbria. In some cases they are bilateral and symmetrical; in others asymmetrical or unilateral.

The pain location and distribution vary with the site of the obstruction.

A. *In Bilateral Strictures at the Uterotubal Junctions.*—Distention pain is present and as a rule mild, being referred to the midline in the suprasymphyseal area. There is no lateral radiation of pain.

B. *In Bilateral Strictures at the Isthmus.*—Pain is somewhat lateral, the midline pain also being present and prominent. The nearer the ampulla to the site of obstruction the more marked is the pain reaction.

C. *In Bilateral Strictures of the Ampulla.*—Pain radiates well out to the sides. The nearer to the fimbria the site of obstruction is located the greater the tendency for pain distribution; pain sometimes radiating to the lumbar region, sometimes down the thigh.

When pain is present on one side only and there are good fluctuations and a positive subphrenic pneumoperitoneum, auscultation may determine the normal tube. The bubbles in the latter instance are intermittent and correspond with the relaxation phase. If no sound is heard on the side where pain is complained of, it is presumptive evidence of an obstruction. In the presence of tubal stenosis, the gas escapes from the fimbriated end in a continuous stream which is only mildly influenced, if at all, by the very much impaired contractions of the tube. There are no silent pauses corresponding with the contraction phases of normal tubal muscle.

It is interesting to note the point at which the patient first complains of pain and when it disappears during the insufflation. Observations were made in cases with tubal closure and apply to instances of tubal strictures. In the cases with peritubal adhesions, pain occurs at a much lower level and is due to stretching of adhesions. In tubal stenosis the pain is due to distention of the proximal portion of the tube and may be maintained throughout the insufflation. As the test lasts but one or two minutes in most cases this is not intolerable. In the vast majority of cases pain was complained of when the pressure was above 110 mm. Hg and was relieved when the pressure dropped 30 mm. Hg or more.

The fluoroscopic examination is an auxiliary help. A subphrenic pneumoperitoneum was not always immediately produced in the strictured tubes where no more than 100 c.c. of gas was used because the amount of gas admitted through the narrow aperture in the tube may

not be sufficient to displace the diaphragm upwards. In exceptional instances the gas may be caught in pelvic adhesions and thus be prevented from rising beneath the diaphragm. Adhesions about the diaphragm as after an old pleurisy or subphrenic abscess may prevent diaphragmatic displacement by the gas. This is a rare occurrence. In general, it was found that when the same amount of carbon dioxide gas was insufflated the depth of the subphrenic pneumoperitoneum was shallower in the case of stenosed and adherent tubes than in normal tubes.

2. OBSERVATIONS FOLLOWING LIPIODOL EXAMINATIONS

Complete tubal closure has been corroborated practically in all cases by the lipiodol examination. The latter was undertaken as a further means of checking the findings and interpretations of the kymographic records in 27 cases of tubal stenosis and peritubal adhesions. A few additional cases had been examined by lipiodol and x-ray elsewhere without a preliminary tubal insufflation. The films were available and served for purposes of comparison. A striking departure between lipiodol injection and insufflation was seen as a result of this comparative study in cases of tubal strictures and peritubal adhesions. In my series only such cases which showed high grade strictures by insufflation were subjected to the oil injection.

Lipiodol has been found in this particular study to possess certain limitations that weaken its corroborative value as compared to laparotomy. For example, in two cases the lipiodol escaped from the cervix so rapidly as not to enter the tubes at all. In 8 cases the lipiodol failed to pass through either tube although insufflation had already shown adherent or stenosed but permeable tubes. Apparently, owing to its thicker consistence, lipiodol was unable to pass through the constricted lumen.

In 13 cases a diagnosis of tubal stenosis was possible from the lipiodol examinations. In 3 cases the tubes were diagnosed as patent but the degree of patency could not be determined. In only one case did the roentgenologist venture the diagnosis of adhesions by interpreting the lipiodol pictures alone. This is not surprising because peritubal adhesions, although impairing the tubal function, do not necessarily constrict the tubal lumen. Lipiodol may pass through the tubes at a relatively low pressure and appear in the peritoneal cavity shortly after its injection. Thus, no information is available as to the question of adhesions. The peristaltic wave is so infrequently demonstrated by the lipiodol plates that little dependence may be placed upon the absence of contractions with that method. It is only after noting the kymographic records obtained by uterotubal insufflation that the salpingograms become significant and then may suggest the possibility of distorted or adherent tubes.

Insufflation after the use of lipiodol in 5 cases failed to permit the passage of gas through the narrowed lumen although it passed before

lipiodol was used. In these cases the oil has a tendency to remain in the narrowed lumen as demonstrated by films which were made at varying intervals from several weeks to several years after the injection. In 2 cases an opportunity was afforded of examining the tubes histologically. Nodular tissue filled with foreign body giant cells was seen in these instances.

If lipiodol is injected without manometric control and the oil globules are seen upon the x-ray film as having entered the peritoneal cavity, nothing more is demonstrated than is shown by the crude method of uterine insufflation as first done by myself and others.

If the injection of lipiodol is not controlled by the fluoroscope and the plate is not made immediately with the cannula in place, one may not be able to say which tube is open and which tube is closed because the lipiodol is scattered in the pelvic cavity and clouds the picture of the tubes. Nor can permeable strictures be determined unless prolonged and repeated fluoroscopic examination is made and supported by x-ray films taken at stated intervals afterward. Occasionally hours and even days may be necessary before the oil shadows demonstrate that the obstruction has been passed. In spite of the numerous plates required for a diagnosis when lipiodol is used the interpretations were often difficult, taxing the skill of an expert.

Distortions of the tubes with appreciable distention will give persistent shadows with lipiodol and suggest perisalpingeal adhesions. These are lesions, however, which may be elicited by bimanual examination. The interpretation of the stenoses is more difficult when they are so tight as to allow only a small amount, i. e., a few drops of oil to escape into the peritoneal cavity. In such cases the shadows may not be distinguished from the droplets retained in the constricted portion of the tube. Even when the oil is actually seen to escape through the tube the question of stenosis is not eliminated unless manometric observations are simultaneously made. The pressure readings are not as diagnostic when oil is used as when gas is used because they are not produced by a uniformly graduated force. The uneven pressure obtained when rubber bulb or syringe is used cannot be compared to a constant flow of gas regulated by a pressure gauge.

With gas, the diagnosis of peritubal adhesions and permeable strictures may be made at once. In cases of doubt where the test has to be repeated, it is both safer and more convenient to use carbon dioxide than lipiodol.

3. EXPERIMENTAL OBSERVATIONS

Normal human tubes as well as the oviducts of the sow which have been removed from the body can be made to survive when immersed in Locke's solution through which oxygen is insufflated. The oxygen may be allowed to pass through the tube lumen as in clinical uterotubal insufflation. Under these conditions the tubes have been shown to exhibit

rhythmic contractions quite identical with those obtained when the tubes are insufflated in vivo.

When the cannula carrying the oxygen is inserted into the fimbriated end of the tube the contractions may be recorded on the kymograph. Records similar to those obtained by the clinical application of the test may be duplicated when the cannula is fitted into the cervix of the specimen of the uterus and tubes.

If the tubes are adherent to the uterus or the ovaries or the intestines the tracings obtained show a striking alteration (Figs. 6 to 13). It

Fig. 6.—Sketch of a specimen showing fundal submucous fibroid and polyp. Peritubal adhesions surround left tube.
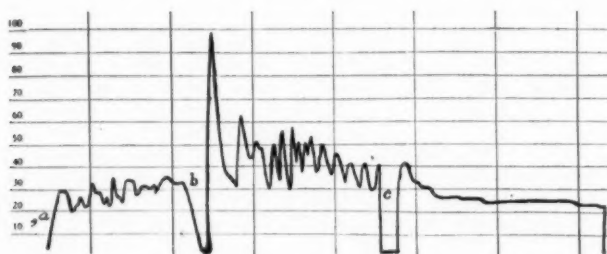
Fig. 7.—*a*, Graph of both tubes; (Fig. 6) *b*, graph of right tube, left tube being held shut between fingers; *c*, graph of left tube (peritubal adhesions) when right tube was held shut between fingers. Experiments shown in Figs. 9 to 15 were made upon this specimen.

should be mentioned that the material used for this purpose must be removed with care so that conditions found at laparotomy are preserved. Special care was therefore taken not to disturb the natural relations of the organs removed. When the kymographic records produced by insufflating the specimens were compared with those obtained by clinical uterotubal insufflations, it was found that the resemblance was most marked.

As the surviving tubes reproduce contractions similar to those obtained in the intact state they offer an opportunity to note what effect mechanical simulation of adhesions and strictures might produce. Accordingly, normal fallopian tubes were insufflated and records obtained
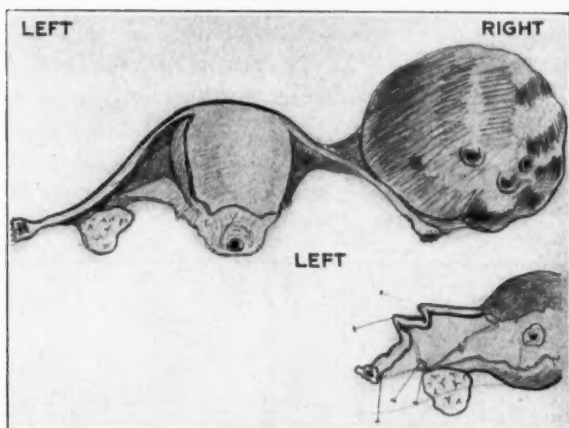
Fig. 8.—Sketch of specimen showing left tube normal in contour and patency. The right tube is adherent along its entire length to the dermoid cyst of the right ovary (size of an orange).
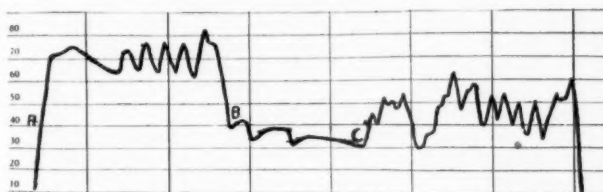
Fig. 9.—*A*, Graph of left tube while right tube is being compressed at uterine end. *B*, Graph of right tube; left tube compressed at uterine end. *C*, Graph of both tubes; compression released.
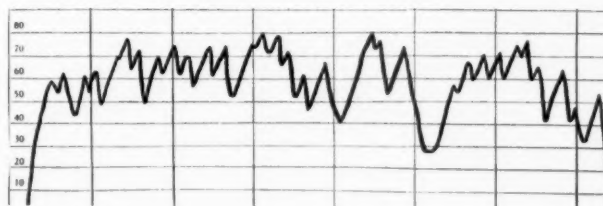
Fig. 10.—Graph of left tube; right tube compressed at uterine end.

Fig. 11.—Graph of right tube; left tube compressed at uterine end.

for comparison.   Peritubal adhesions and tubal stenosis were then arti-
ficially produced by: (1) immobilizing the tubes with pins; (2) con-
stricting the tubes with weights; (3) constricting the tubes with clamps;
(4) constricting the isthmus alone after the ampulla was excised; and
(5) twisting the uterus so as to constrict the tubes.

1. *Effect of Immobilizing the Tubes With Pins.*—The tubes were placed upon a
cork plate and were transfixed by fastening pins through the serosa at several points
(Fig. 14).
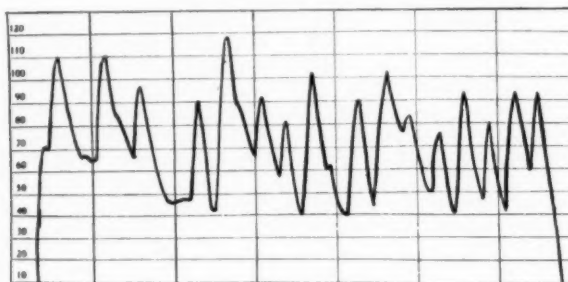
Fig. 12.—Graph of both tubes; marked contractions after the tubes had been irritated
by heat and pinching.
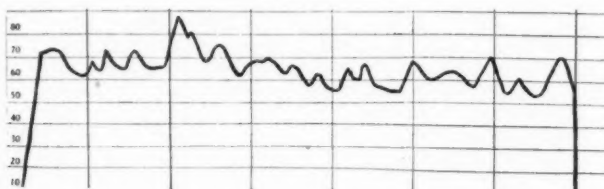
Fig. 13.—Graph of right tube; left tube transfixed by pins as in diagram.
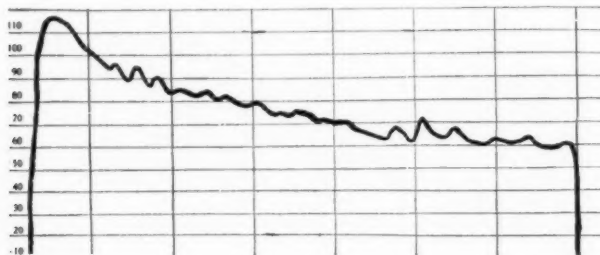
Fig. 14.—Graph of transfixed left tube; right tube is compressed at uterine end.

If the tubes are transfixed by pins without causing distortion or angulation, the
initial rise in pressure may not exceed 100 mm. Hg but no well marked fluctuations
are seen.   The tubes do not undergo peristaltic or pendulum motion and the waves
of contraction are inhibited.   This is graphically represented on the kymograph.

If only one side of the tube is transfixed, i. e., along the mesosalpinx leaving the
opposite surface free, the tube exhibits normal contractions and the initial rise of
pressure is not unduly high.   The gas in the latter instance flows out of the tube in
intermittent bubbles instead of in a constant stream which is observed when the tubes
are held down by adhesions or are the seat of well marked strictures.

If the isthmus alone is pinned down and the remaining tube is left in its normal condition, only a rare contraction, if any, occurs. If part of the isthmus is left free, irregular and infrequent contractions occur. With the isthmus free and the ampulla pinned down the type of tubal contractions is but little affected; a slight irregularity in rhythm may be noted.

When the pins are removed if the experiment is not delayed too long after removal of the organs and while they are still in a good state of preservation, they may regain their former contractility and describe curves in a rhythmic fashion.
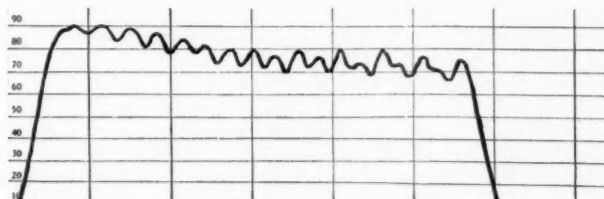
Fig. 15.—Graph of right tube; left tube is compressed at uterine end.
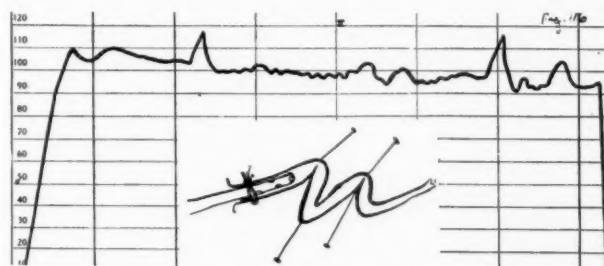
Fig. 16.—Showing graph of experimental duplication of peritubal adhesions, showing cannula in the fimbriated end of human tube, and graph of tube transfixed by pins as in diagram.
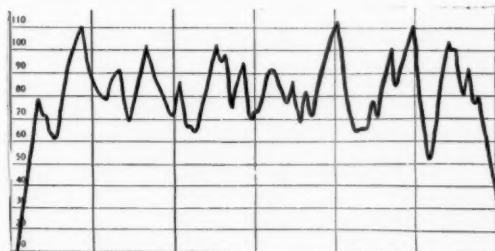
Fig. 17.—Graph of tube after the pins were removed one hour and fifteen minutes from the beginning of the experiment.

2. *Effect of Constricting the Tubes With Weights.*—The artificial duplication of an internal stricture is more difficult to produce than external constriction. The latter may be actually produced by applying weights or clamps to the tubes.

Applying weights to the tubes was found to produce an elevation of the pressure at which contractions were maintained and an irregularity in the rhythm and depth of the contractions directly proportional to the amount of constriction produced. When the lumen was but slightly obstructed, the initial pressure rose to about 100 mm. Hg; the contractions became infrequent and irregular but maintained a fluctuation range even as high as 40 mm. Hg. With increased weight the constriction could be augmented to the point of complete tubal closure.

3. *Effect of Constricting the Tube With Clamps.*—Constriction of the tube was reproduced by applying clamps of the Murphy regulating type at different points along its length. The character of the kymographic curve resembles in appearance that of a clinical pathologic stenosis of the tubes (Fig. 15).
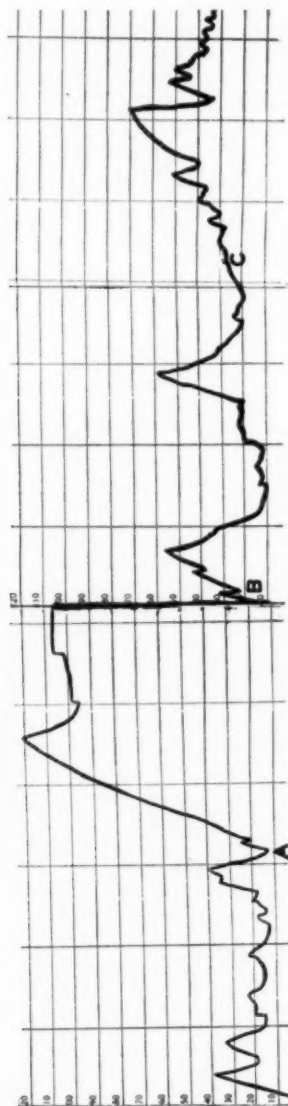
Fig. 18.—Experimental duplication of tubal stenosis and adhesions; uterotubal insufflation of pig's tube at interestrus. *A,* Isthmus compressed by clamp without complete closure. *B,* Isthmus transfixed without distortion as in diagram. *C,* Ampulla then transfixed as in the diagram (Fig. 19). (Pins removed from isthmus.)

It has been found in the course of experiments that there is a decided difference between isthmic and ampullary strictures. This depends upon the specifically different type of contractions each of these segments possesses under normal conditions.

In the case of human tubes, the intramural portion and isthmus appear to exhibit the most marked contractions. These may be observed when insufflation is directed toward the abdominal end or the uterine end of the tubes and parts of the tube are progressively excised. If the isthmus is removed leaving the ampulla in-

tact (fimbriated insufflation) the contractions are shallower and may even be absent.

In one clinical uterotubal insufflation I had the opportunity of noting the type of curves produced when only one ampullary fimbriated portion was present. This portion had been implanted into the uterine horn, the isthmus having been excised

Fig. 19
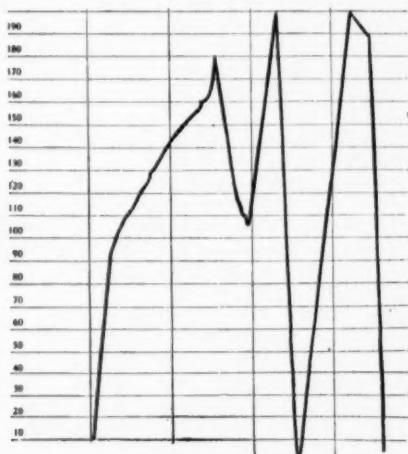
Fig. 20.

Fig. 19.—Pig's oviduct and uterine horn transfixed at the isthmus and ampulla.
Fig. 20.—Graph of the ampulla after a tubouterine implantation. Insufflation before operation July 19, 1930. Nonpatency.

Fig. 21.—Lipiodol examination before operation August 23, 1930; showed both tubes to be completely blocked at the uterine end. Same case as Fig. 20.

and the other tube removed for advanced nodular salpingitis. No contractions occurred and the pressure maintained was not unduly high (Fig. 16).

Contractions are exhibited by the tube whether the insufflation is directed toward the abdominal or the uterine end. In the pig the frequency of the tubal contractions varies, however, with the estrus interval. Thus the contractions obtained by utero-

tubal insufflation at estrus are regular and occur at a rate of about 15 to the minute, whereas only irregular, less frequent contractions occur when fimbriated insufflation is performed. The reverse holds for the interestrus interval.[*] These results have not been studied systematically in the human tubes.

Experiments were carried out on intact tubes in which the isthmus and ampulla were clamped separately, and upon the isthmus alone after the ampulla was removed. Constricting either the isthmus or ampulla resulted in an elevation of the pressure which was sustained as long as the gas flowed through the tubes. Contractions were
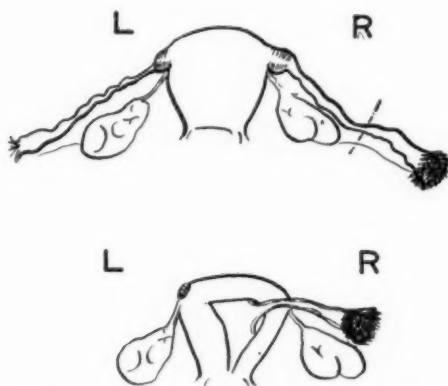
Fig. 22.—Operation October 7, 1930. Both tubes were found obliterated by nodules at their uterine end. The left tube was removed. The nodular portion of the right tube was resected and the ampulla with the fimbriated end, tested for patency by syringe and medicine dropper, were implanted into the fundus. Same as Fig. 20.

Fig. 23.—Insufflation after operation November 24, 1930; showed the implanted ampullary portion of the right tube to be patent at a pressure of 145 mm. Hg but there were no contractions. A second insufflation done immediately afterwards gave a pressure of 98 mm. Hg with similar type of curve. Same as Fig. 20.

absent for the most part or at times infrequent and irregular depending upon the degree of stricture produced. The paralyzing effect upon the contractions was more marked when the isthmus was clamped than when the ampulla was constricted. The same result was obtained when the isthmic stump was clamped after the ampulla had been excised.

4. *Effect of Constricting the Tubes by Twisting the Uterus.*—In order to note the effect produced by tortion of the tubes upon both pressure and contractions, the

uterus with the tubes attached was twisted upon itself. When the uterus was twisted to 180 degrees, there was little effect noted. When it was twisted to 270 degrees the pressure at which contractions were maintained was about 20 mm. Hg higher; contractions, however, continuing as before. As the amount of tortion was increased the contractions became less frequent and more shallow until, when the uterus was twisted to 360 degrees, closure resulted and the pressure exceeded 200 mm. Hg.

SUMMARY

1. The diagnosis of nonpalpable tubal adhesions and tubal stenosis can be made by uterotubal insufflation with the aid of the kymograph. It is based upon the fact that tubal contractions in the presence of these lesions are completely absent or markedly changed. Observations were made at laparotomy where these lesions were found affording an opportunity of checking the insufflation findings. Characteristic curves were produced.

2. In the presence of tubal stenosis, whether of extrinsic or intrinsic origin, the initial rise of pressure was as a rule well above 100 mm. Hg. Instead of dropping sharply and exhibiting oscillations the curve produced was rounded and the descent gradual. Fluctuations were absent as a rule.

3. In the presence of peritubal adhesions without constriction of the lumen, the pressure was less elevated. The contractions were infrequent, irregular or shallow and at times entirely absent, depending upon the degree of immobilization produced.

4. The location of pain elicited during the performance of the test as well as the auscultation findings were found to vary with the site of obstruction.

5. Roentgenologic examination of the tubes after lipiodol injection proved of less value than laparotomy in checking the insufflation findings of peritubal adhesions and tubal stenosis. The disadvantages of the oil in this respect were due to: (1) its rapid escape from the cervix in some cases; (2) its inability to pass high grade strictures in most cases, and (3) its tendency in the strictured tubes to produce foreign body reactions.

6. Insufflation of the excised but surviving uterus and tubes reproduce curves similar to those found by clinical uterotubal insufflation where adhesions and strictures were present. By artificially reproducing immobilizations and stenosis of the tubes, the paralyzing effect upon rhythmic tubal contractions and tubal peristalsis was also demonstrated.

911 PARK AVENUE.

THE INFLUENCE OF AGE AND RACE ON THE DURATION OF LABOR

C. H. PECKHAM, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, the Johns Hopkins Hospital and University)

IT HAS long been felt that from a strictly physical point of view, the young woman of fifteen to twenty years of age makes the most satisfactory obstetric patient, and that a definite correlation exists between increasing age and various abnormalities and accidents of pregnancy, labor, and the puerperium. In recent communications the author has drawn attention to the fact that with increasing age the maternal and fetal mortality, as well as the incidence of operative deliveries, becomes considerably greater. The purpose of this study is to investigate the influence of age on the duration of labor, and particularly to ascertain whether any differences in this respect exist between the white and black races, as the two about equally make up the population of this clinic.

For this purpose we have used the same material as in the above mentioned articles; namely, a series of 15,370 consecutive deliveries, premature and fullterm, occurring in the Johns Hopkins Hospital during the period from January 1, 1907, to December 13, 1929. Except for computing the mean duration of labor the patients delivering prematurely have been discarded, as well as those delivered by cesarean section, and a few in whom the case records were lacking in definite information as to the duration of labor or the age of the patient. There remains a total of 13,658 patients, delivered at or near term through the birth canal, and divided by color and parity into the groups shown below.

	WHITE	BLACK	TOTAL
Primiparae	3742	3880	7622
Multiparae	3352	2684	6036
Total	7094	6564	13,658

An analysis was first made of the total cases in the series. The mean duration of labor in both primiparae and multiparae is longer in the black than in the white women. Thus the average primiparous labor in the white lasts 16.57 hours as contrasted with 17.66 hours in the black race, while figures of 10.91 and 12.49 hours obtain for the two groups among the multiparae.

The difference between the two races and the effect of increasing age is graphically illustrated in Fig. 1. From this it will be seen that in the white race the duration of labor tends to increase, although not strikingly, in the older age groups, both primiparae and multiparae. Thus, while the mean duration in white primiparae remains approximately 16.7 hours from the age of seventeen to thirty, it rises thereafter and in

women above the age of thirty-five reaches 18.05 hours. A similar, though less marked tendency is observed among the multiparae. Among the black women the rise in the later age groups is much more significant. Thus, in the group of black primiparae aged twenty to twenty-four, the mean duration of labor is 17.67 hours, but rises thereafter so that

FIGURE 1
DURATION OF LABOR ACCORDING TO AGE
TOTAL CASES

FIGURE 2
DURATION OF LABOR ACCORDING TO AGE
NORMAL PELVIS ONLY
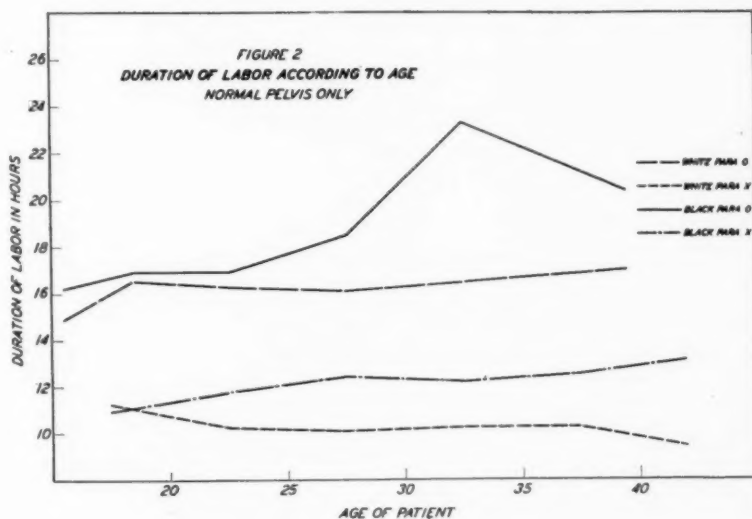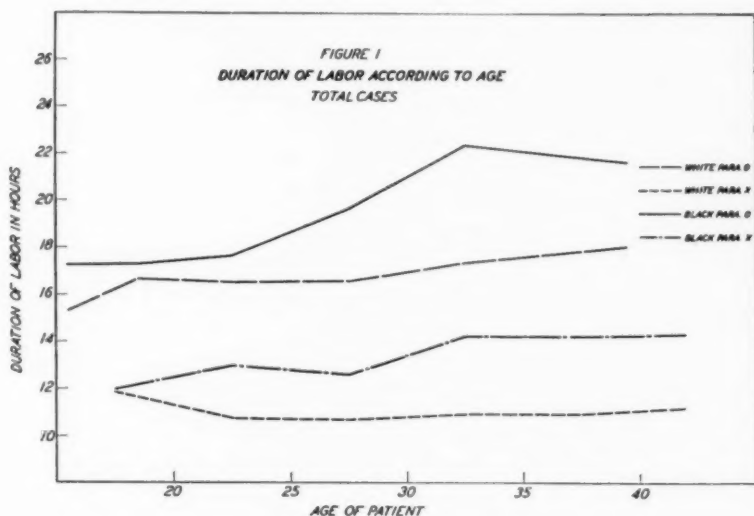
above the age of thirty-five years a figure of 21.67 is reached. A similar trend though again less marked, was found among the multiparae of this group.

Fig. 1 then, indicates an apparently significant racial difference in the duration of labor. In searching for an explanation of this rather

unexpected finding, it at first seemed probable that the higher incidence of contracted pelvis among the blacks might play a rôle in causing prolongation of their labors, since some degree of pelvic abnormality is observed in 45 per cent of the black as contrasted with less than 20 per cent of the white women in the clinic population.

Accordingly, a similar analysis was made of the material at hand omitting all cases of contracted pelvis, and excluding outlet as well as inlet contractions. The results of this study are illustrated in Fig. 2. Again, in the black primiparae, the mean duration of labor is significantly prolonged over that of the white, particularly in the older age groups (above thirty years), while in the multiparae there is at least a two hour difference from the age of twenty-five on.

FIGURE 3
DURATION OF LABOR ACCORDING TO AGE
CONTRACTED PELVIS ONLY
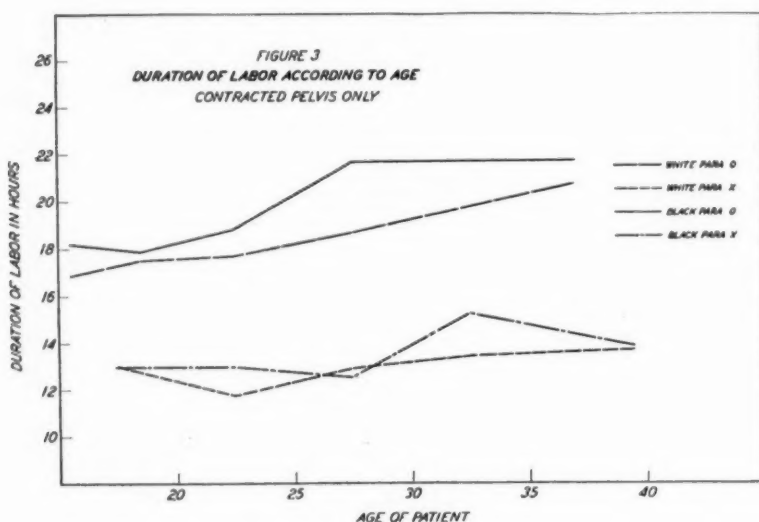
It will also be noted from Fig. 2 that in the white patients, both primiparae and multiparae, there is almost no increase in the duration of labor in the older age groups, the figure of seventeen hours for the elderly primiparae (above thirty-five) being only nine-tenths hours above that of the age group twenty-five to twenty-nine, the low point for this group of cases above the age of sixteen. However, in the black women there is a notable tendency toward longer labors in the higher age groups, which is more pronounced among the primiparae than the multiparae.

Fig. 3 indicates that in the group of patients with contracted pelves the racial differences are less marked. However, the colored primipara still has a longer labor than the white, whereas the difference between the multiparae of the two races is probably too small to be significant. Both races here show a tendency toward longer labor with increasing age. Indeed, the primiparae aged thirty-five and over in both races have a

mean labor lasting about three hours longer than in the age group twenty to twenty-four.

It may be stated that the entire series of cases regardless of type of pelvis, indicates that those labors terminated by some operative procedure are constantly several hours longer than in the group of spontaneous deliveries. This is true of the multiparae as well as primiparae, and is not surprising. However, it seems noteworthy that in the black race the difference in the length of labor in operative over spontaneous deliveries is constantly greater than that observed among the whites.

In our effort to arrive at the true differences in the duration of labor according to age and race, it next seemed advisable to omit as a complicating factor all operative deliveries. Fig. 4 presents the average labors

FIGURE 4
DURATION OF LABOR ACCORDING TO AGE SPONTANEOUS DELIVERY
TOTAL CASES
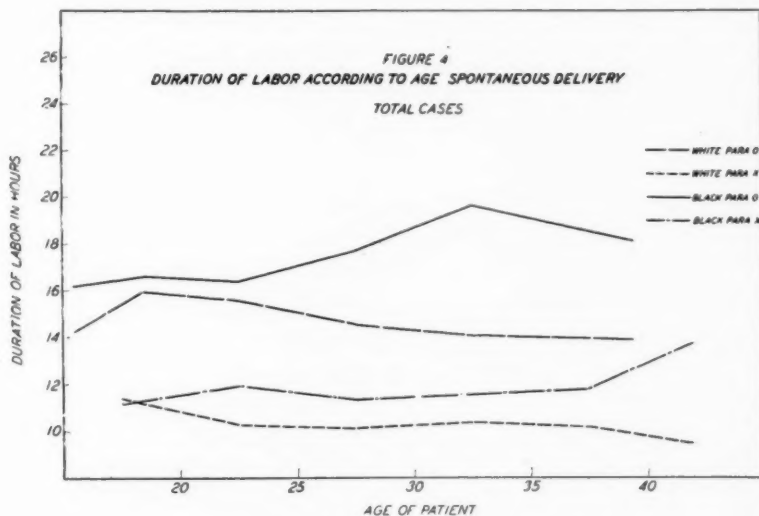
in the different age groups terminating without any operative interference. The racial differences hitherto observed are still found to persist, and indeed among the primiparae over twenty-five years of age are greater than when the operative groups were included. No increase in the duration of labor with age is observed among the white women and in fact there is a steady trend downward in the older age groups, as it is found that the mean duration in primiparae over thirty-five is 2.06 hours less than those aged seventeen to nineteen, the group with the longest mean labor for this type. Among the black women, however, the duration of spontaneous labor is still increased in the older age groups, and more noticeably so in primiparae than multiparae.

Fig. 5 would appear to indicate most accurately the real effect of race and age on the duration of labor, for here only those cases terminating spontaneously and with normal pelves are considered. The mean duration of labor among the black multiparae is 11.20 hours, a figure 1.28

hours above that obtaining in the white, and with multiparity no tendency is noted toward the prolongation of labor by increased age in either race, indeed, in the black women above the age of forty a definite increase has taken place. The number of cases on which this figure is based are, however, so small, as to make one suspect that it may be due to a sampling error. The case for the primiparae is, however, quite different. The labors in the black women are longer throughout, and significantly so after the age of twenty-five. In the higher age groups the mean duration falls in the white and rises in the black patients, so that after the age of thirty-five is reached the difference becomes 5.31 hours.

The average length of labor, based on a large series of cases at or near

FIGURE 5
DURATION OF LABOR ACCORDING TO AGE SPONTANEOUS DELIVERY
NORMAL PELVIS ONLY
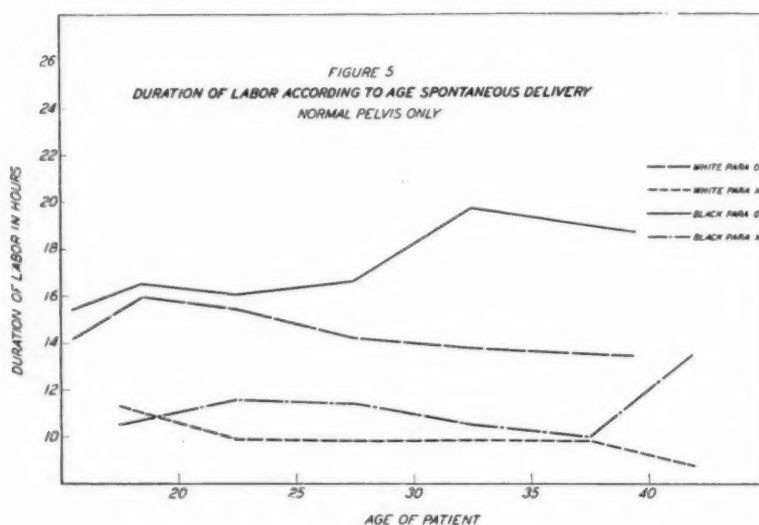
term, but excluding cesarean section, is approximately seventeen hours and forty minutes in black primiparae, as contrasted with sixteen hours and thirty-four minutes in the white, whereas in the multiparae we find figures of twelve hours and twenty-nine minutes and ten hours and fifty-five minutes for the two races, respectively.

The length of labor is relatively little affected by degrees of pelvic contraction which permit delivery through the birth canal. Thus, in white primiparae with normal pelves the mean duration is 16.25 hours, as contrasted with 17.91 hours where some degree of contracted pelvis exists, while in black primiparae figures of 17.03 and 18.49 hours obtain. Similar differences are found in the multiparae of the two races.

DISCUSSION

An analysis of the effect of race and age on the duration of labor in a series of 13,658 consecutive deliveries at or near term reveals a sur-

prisingly constant difference between white and black women. Regardless of age or parity, the black patient has a longer labor than the white. The difference is not particularly marked in women under twenty-five years, but after this age it increases to several hours. The explanation for this phenomenon is not clear. It seems evident, however, that it is not due to the higher incidence of contracted pelvis among the blacks, for a study of the patients with normal pelves shows the same disparity as when only those with contracted pelves are considered. This racial difference becomes even more difficult to explain when one recalls the increased malleability of the fetal head and the smaller weight of the infants in the black race. Thus, in a series of 2,000 deliveries at or near term, and equally divided between the two races, the mean weight of the black and white infants was 3155.9 gm. and 3379.9 gm., respectively, a difference of 224 gm. or 7½ ounces. The patients in this series, however, represent mostly the dwellers in the tenement districts of a large city, and it seems likely that such an environment has produced degenerative changes in the black race, which is increasingly incapable of easy childbearing.

Our figures show that in both races there is a tendency for the duration of labor to increase with advancing age, a phenomenon much more marked in the black than in the white women. Thus, a consideration of the total patients in the series reveals an average labor of 15.30 hours in white primiparae under the age of sixteen which rises to 18.04 hours in women thirty-five years or older, whereas in the blacks of corresponding age, figures of 17.24 hours and 21.67 hours respectively obtain. The same tendency, although not so marked, obtains in the multiparae of each group. On the other hand, when our consideration is limited to women with normal pelves, almost no rise in mean duration is noted among the whites, although labor is definitely prolonged in the older age groups in the black race.

A consideration of the cases in the series delivering spontaneously, including both normal and contracted pelvis, shows a decrease in the mean duration of labor among white women, both primiparae and multiparae. Thus in white primiparae aged seventeen to nineteen, the average labor lasts 15.97 hours, while in similar patients aged thirty-five or over, it is only 13.91 hours. On the other hand, a rise in mean duration still occurs in the blacks of older age as is evidenced by figures of 16.20 hours and 18.13 hours in primiparae below seventeen and above thirty-four years, respectively.

Finally, when only those patients with normal pelves who deliver spontaneously are included, we again find a definite drop in the duration of labor among whites of the higher age groups, although among black primiparae of similar age an increased duration of labor is still noted.

This study indicates that in still another way, i. e., length of labor, the black woman is a less satisfactory obstetric risk than the white. Since in

an accompanying article we will demonstrate that fetal mortality increases directly with the duration of labor, it seems probable that the increased duration among black women accounts to some extent for the higher fetal mortality in that race.

Contrary to the general belief, our figures show that there is very little increase in the duration of labor with advancing age among white women. Indeed, in those delivering spontaneously a decrease in mean duration is observed in the older age groups. Including all cases, spontaneous and operative, normal and contracted pelvis, the mean duration of labor in primiparae aged thirty-five or over is only 1.38 hours greater than that recorded for those between seventeen to nineteen years of age, while for multiparae even less increase is seen with age. Consequently, it seems probable that the increased operative incidence and higher fetal mortality observed in the obstetrically elderly woman is chiefly to be explained in terms of rigid soft parts affecting the second stage of labor, and that the first stage progresses as normally and approximately as rapidly as in the younger woman. This reasoning, however, does not apply to the black race where definitely prolonged labors are observed with increasing age.

CONCLUSIONS

1. An analysis has been made of the effect of age and race on the duration of labor in a series of 13,658 consecutive deliveries at or near term.

2. Black women, both primiparae and multiparae, and regardless of age, have consistently longer labors than white.

3. In both races, a consideration of total cases reveals an increased duration of labor in the older age groups, which however is more marked among black than white women.

4. Omitting cases of contracted pelvis, this age increase persists in the black but almost disappears in the white race.

5. Considering only those cases delivering spontaneously, the duration of labor tends to fall with advancing age in white patients, even primigravidae, although it increases in black women regardless of parity.

NOTE: A series of tables giving in detail the statistical data on which this paper is based has been omitted owing to lack of space.—*Editor.*

CLASSIFICATION AND TREATMENT OF DYSPAREUNIA*

Max D. Mayer, M.D., New York

(From the Gynecological Service of the Mount Sinai Hospital)

THE arrangement on the Gynecological Service whereby each morning clinic of the Out-Patient Department is reserved for the study of a special group of cases, has made it possible to concentrate the series of cases of dyspareunia.

The treatment of dyspareunia must be individualized because the cases do not conform to a single type. They vary as to cause, as to the individuals, and as to the domestic situation.

In general, the causes may be classified as follows:

1.—Organic:

(A) Introital: rigid hymen; reflex spasm from trauma or infection or both; operative overcorrection of plastics; atrophy of the senile type and that following x-ray treatment; kraurosis; urethral, e. g., caruncle, urethritis, cystitis; anal fissure; neuritis of the pudic nerve.

(B) Pelvic: diseased adnexa; shortened parametria; prolapsed ovary.

2.—Psychogenic:

(A) Initial dyspareunia: fear of injury (narcissistic type); fear of pregnancy; as a symptom of severe neurosis; as a symptom of psychosis.

(B) Secondarily acquired dyspareunia: fear of pregnancy; hysterical manifestation (of a negative attitude toward the husband, equivalent in many cases of frigidity).

3.—Combinations of Organic and Psychogenic:

The above may be combined in any quantitative relationship: (a) Where an organic lesion is secondarily invested with a mental significance, with emphasis on the factor of morbid gain. (b) Where a vaginal spasm has led to secondary organic changes, as for instance, the results of trauma from attempts to overcome it.

DIAGNOSIS

First importance should be given to the history; not only the material, but the way of eliciting it. It should go without saying that the first step is to estimate the personality of the patient and make every effort to get a certain measure of confidence before proceeding with the history itself. In addition to the ordinary gynecologic history, it is essential to determine the familial setting, the developmental history, other complaints, and other experiences in the past. Among the most important of the facts in the present history are the severity, duration, onset, the patient's attitude toward the complaint and to her mate, the previous attempts at treatment, the frequency, duration, position, etc., of coitus, the presence or absence of orgasm. One should realize the transference situation in taking the history, and that often there is an initial attitude toward the doctor as an enemy who threatens to duplicate a painful situation and who somehow seems to be in alliance with the husband, against whom the symptom may be a defense.

TREATMENT

This will, of course, depend upon the type of dyspareunia and its cause. It may be classified as follows:

1. Prophylactic: May I mention at this point that Dr. Dickinson in his articles and numerous discussions on the subject of premarital instruction as well as in his excellent study of *A Thousand Marriages*, has correctly emphasized the importance of prophylaxis, and I can do no better than to refer you to his recommendations. Unfortunately, the gynecologist, both in clinic and office practice, sees the majority of cases when it is far too late for prophylaxis.

2. Actual Treatment: The actual treatment should be radical. If the cause is mental, the treatment should be mental, though it must be understood that this does not preclude local measures and that the patient may very well attribute a cure to these local measures. The treatment of the husband in these cases may be of great and even paramount importance. Incidentally, there is a high incidence of gentle, timid and inexperienced men, often relatively impotent, among the husbands of these women with primary dyspareunia. Perhaps this is due, in part, to their unconscious selection, on the somewhat mistaken assumption, that a gentle person would hurt them less; in part, it is the result of far more complex, deep-seated, psychologic reasons that I cannot enter into now, except to state that they are associated with their castration anxiety and envy of the male.

A. Rigid Hymen: The hymen will have to be stretched or cut. It might often seem simpler to cut it, yet actually, it is more practicable to stretch it by gradual dilatation. In cases of local trauma, vulvitis or vulvovaginitis, the inflammation must be treated before any attempts at stretching are made. One cannot over-emphasize the need for the most scrupulous care to avoid the slightest pain. Douching is in most cases inadvisable. A useful method is to insert an endoscope, and through this, a strip of gauze impregnated with Lasar's paste. This keeps the surfaces apart and dry and has the additional advantage of preventing any attempts at coitus. It should be changed daily.

B. Postoperative. Postoperative dyspareunia is the result of various types of operative misjudgments. (1) Too high a perineum of the shallow type may act as a thin commissural band which has the effect of a hymen. (2) Too narrow a vagina as the result of sacrificing too much mucosa in the anterior plastic. (3) Too tight levator sutures catching the muscle bundles with the consequent constriction ring at the vagina. (4) Too tight a vagina left after a vaginal hysterectomy. The treatment will depend upon the severity of the case. Some cases respond to non-operative dilatation which should be tried. Others require the so-called reverse plastic in which a nice judgment must be exercised to maintain the proper balance between the coital and supportive functions.

C. Atrophy: In the senile type of atrophy the relative infrequency of coitus plays a rôle and it seems important to prevent further shrinking by the wearing of vaginal plugs of appropriate size for rather considerable periods at regular intervals. Good lubrication is very important, and in douching one should avoid the stronger astringents. The hormonal treatment of these cases is feasible, but at present not practicable.

D. In the urethral type of dyspareunia, it seems advisable to toughen the meatus

with proper applications, but more important is instruction in altering the coital position to avoid catching the urethra underneath the pubic arch. ''A posteriori'' sometimes answers the purpose very well.

E. In the case of dyspareunia due to diseased adnexa. In addition to the usual general, hydrotherapeutic and thermal method, the *colpeurysis* treatment with mercury is sometimes very efficacious. If because of the great chronicity of the condition, coitus cannot be interdicted, the following position should be advised: After intromission in the lithotomy position, the woman's thighs are fully extended and approximated, her knees inside the slightly separated knees of the man. This gives the minimum penetration, the minimum pelvic pain without sacrificing mutual stimulation.

F. In the cases of prolapsed ovary, the insertion of a Hodge pessary worked very well in two cases.

G. In the cases of dyspareunia associated with shortened parametria, the treatment is more or less like that with diseased adnexa.

PSYCHOGENIC

The treatment of psychogenic dyspareunia commands extended attention. Obviously, one cannot enter here into the intricacies of the dynamics of its genesis. In the severer cases, this is a task for the specialist. It is very important for the gynecologist to recognize and differentiate those cases in which he can reasonably expect to get a good result from the suggestive measures at his disposal and those which he had better refer to a psychotherapist.

This much should be said: that the majority of cases of dyspareunia coming to the gynecologist are primarily psychogenic, although all the cases have some psychologic factors. The more these factors are taken into account, the more efficacious the treatment. It is of great importance to interview the husband, as obviously he may be the one to require attention.

In approaching the treatment of psychogenic dyspareunia, it seems advisable for the time being, to forget anatomic considerations and consider the individual. The cases may be simply grouped into:

1. The mild, in which there is a somewhat excessive reaction to an unfavorable situation, as for instance, an inept, inexperienced husband, an unusually thick hymen, a timid individual; the patient is cooperative and has insight. In these cases, the treatment can be rapid and one can very well combine local treatment with psychotherapy in the following way:

This method embodies the dynamics of the psychotherapeutic cure without any attempt to give the patient conscious insight. In this respect it is similar to many forms commonly used in medical treatment, but differs in that the physician is more or less aware of the mechanism.

At the first visit the patient is interviewed, (mostly listened to) and preferably not examined. When an examination is made, it is but an inspection. There should be no pain. The doctor concentrates his efforts in gaining the woman's confidence.

An endoscope is inserted through which a wick of medicated gauze is passed and left in. At subsequent visits very gradual and mechanical dilatation, combined with the local treatment, finally permits the easy introduction of a small vaginal speculum. This is replaced by a series of graduated test tubes, up to 1¼ in. in diameter. Then the patient is shown how to introduce this test tube herself, which she does with ease. Then she is given the test tube and instructed to introduce

it herself at home for several days. The husband is then interviewed and instructed, and all treatment tentatively discontinued before the couple make any attempts at coitus.

The underlying principle is the establishment of confidence and the transference through which the fear, resentment and anxiety are partially overcome. This permits the alleviation of the local condition by a mechanical means which is presently replaced by an instrument with phallic significance. The patient is encouraged to be cooperative in its introduction. The treatment is then terminated and the patient returns to her coital function with an altered point of view. I do not think one need fear the danger of instituting autoerotism, principally because these women are not yet vaginally erotised.

2. The severe. In severer cases we see an inadequate response to a not unusual situation; there is no disproportion; there are other manifestations of a neurotic make-up; cooperation is not complete and insight is often lacking. In these cases, the treatment should be psychotherapeutic purely, up to the point where the patient is herself desirous of instituting local treatment.

3. The extremely severe forms, as for instance, in the cases of persistent virgins for many years; we must be extremely cautious. They are frequently psychopathic personalities. Interference here is not without considerable danger of a complete breakdown and even suicide.

ACQUIRED DYSPAREUNIA

In the first group resulting from fear of pregnancy, one may combine a brief psychotherapy with adequate contraceptive advice. In the group in which the dyspareunia is a result of a negative reaction against the husband, local treatment is of no avail. Brief psychotherapy of the suggestive type is almost always doomed to failure. Prolonged psychotherapy only offers a reasonably fair prognosis as far as the dyspareunia is concerned; though the prognosis is poor, quoad frigidity.

Combinations are treated after a careful evaluation of the factors. I do not wish to convey the impression that the rapid treatment, or for that matter, any treatment offers a guarantee for cure. Many cases do not respond rapidly. One cannot emphasize too strongly the necessity for individualization of the cases as well as the necessity for the utmost patience.

Dyspareunia, then, is due to a variety of causes, that manifests itself in all degrees of severity. The causes may be organic or mental or combinations of both. Treatment should be instituted in both directions. The condition may seem a minor one, when it is really of major importance in the life of the individual. There is a need for marked individualization of the cases. The prognosis varies considerably. It is least favorable in those cases which show absolutely no organic manifestation. As far as psychotherapy is concerned, in the mild cases, simple suggestion seems best; in the severer cases, formal psychotherapy and in the most severe cases, as in the case of persistent hymen over many years in a psychopathic person, "*noli me tangere.*"

Training in psychoanalysis has a triple usefulness in the treatment of these cases: (1) It offers the road to the possible understanding of the complex mechanisms through which these conditions arise. (2) It

offers a technic for intelligent listening in the eliciting of an adequate history. (3) In very carefully selected cases, it offers a radical therapy which attempt to combine the removal of symptoms with an adjustment or readjustment of an unhappy individual.

1150 FIFTH AVENUE.

A CASE OF MARKED HYDRAMNIOS IN THE FIFTH MONTH OF PREGNANCY*

E. EVERETT BUNZEL, M.D., NEW YORK, N. Y.

MRS. W. P. B., aged twenty-six, white, was seen by me in her first pregnancy in July, 1926. Her menstrual history had always been normal of the twenty-eight day type. Her past history had been insignificant except for measles as a child and an appendectomy in 1918. Her expected date of confinement was estimated to be about February 24, 1927.

At seven months, an external cephalic version was done. She was delivered at term by low forceps of a 7 pound 14 ounce baby girl, after a labor of seventeen and one-half hours. She made an uneventful recovery, nursing the baby several months.

On November 4, 1931, she came to consult me in her third pregnancy, having had another baby girl in September, 1930. This pregnancy was normal, the labor short and easy, and this baby weighed 7 pounds 14 ounces also. Although she nursed for seven months, up to April, 1931, she menstruated regularly after the first two months. Her last period began on May 25, and lasted the usual five days. Therefore at the time she came to me she had just completed the fifth month of her third pregnancy.

In the early months of this pregnancy, as with the other two, she had mild nausea and vomiting and under the care of a local physician out of town, noticed nothing unusual until the middle part of her fourth month. At this time both she and the doctor thought her abdomen was larger than it should be for the period of gestation. The uterus from that time on continued to grow rapidly in size and the patient had increasingly severe backache and discomfort, to such a marked degree that she was unable to sleep well even propped up in bed and with three allonal tablets at bedtime. She had felt life on October 16 (at four and one-third months).

On physical examination on November 4, her face was flushed, her eyes sunken; she looked tired, and her hands were bluish in color. The abdomen appeared to be the size of a full term pregnancy or more. The skin of the abdominal wall was suffused, and blanched on touching it. It was impossible definitely to outline the uterus as it was flaccid and occupied the entire abdominal cavity, but there was a distinct fluid wave throughout. The abdomen measured 106 cm. in diameter at the level of the navel. No fetus or fetal parts could be palpated, nor could a fetal heart be heard. However, I could hear fetal movements. The lungs and heart were normal and the blood pressure 108/70. Mouth temperature was 99° and pulse 130. The cervix was soft, ¾ of an inch long and admitted only the tip of a finger. No presenting part could be felt. A diagnosis of acute hydramnios was made.

I advised admission to the hospital at once because of the patient's extreme discomfort. A blood count showed: Red blood cells 3,730,000, hemoglobin 74, white blood cells 10,200, polymorphonuclear leucocytes 83 per cent. Blood was Type 1 (Jansky).

X-ray of the abdomen done the afternoon of admission, November 4, 1931, was somewhat indistinct because of the hydramnios, but a good film was obtained the next morning with the following report: "Films of the abdomen demonstrate an

enlarged uterine shadow suggesting polyhydramnios. Within the shadow of the uterus we see a single fetal skeleton. The size is greatly out of proportion to that of the uterus. We see no evidence of fetal anomaly. The size of the fetal shadow suggests a four to five months' pregnancy.''

The problem at this time therefore, was to determine if it would be possible to comfort the patient sufficiently to permit continuation of the pregnancy. But repeated doses of morphia and luminal, given hypodermically, were without sufficient effect to justify this procedure. The abdominal discomfort, backache and dyspnea were so marked that the patient had to be propped up in bed almost into an erect position. And in addition she could not sleep. Therefore after forty-eight hours' trial it was decided to interrupt the pregnancy.

On November 6, 1931, under nitrous oxide because of the patient's nervousness and apprehension, and after preparation of the vulva and vagina with iodine and catheterization of the bladder, pelvic examination showed the cervix to be soft, about ½ inch in length and readily admitting a finger through the internal os. The cervix was gradually dilated until two fingers could be introduced. A stilette was then passed through the cervix and the membranes were ruptured high up at 9:40 A.M. Keeping two fingers in the cervix, the amniotic fluid was allowed to drain off very slowly over a period of fifty minutes. During this time, the uterus began to contract irregularly, and the patient's pulse dropped from 128 to 100 at which level it remained throughout the labor. The measured amount of amniotic fluid was 11 quarts. After complete drainage the abdomen was tightly bound. The contractions continued irregularly, and at 11:30 A.M., one hour later, there was a sudden gush of blood per vaginam completely saturating the vulval towel. From this time on, there was a small amount of oozing of blood from the vagina. Three doses of pituitrin were given of minims three, four, and five at 12:30, 1:00, and 2:15 P.M. respectively until the uterine contractions were definitely regularly established. Eventually, a vertex presented completely covered with membranes. These were ruptured and a very small amount of amniotic fluid escaped. The fetus was delivered at 6:11 P.M. and two minutes later came another fetus by the breech, considerably smaller than the first. The second fetus was markedly discolored and the cord of the second fetus was very much smaller than that of the first. There was very little bleeding after the birth of the fetuses, but the uterus had little tone to it and did not contract well.

At the end of half an hour, the operator's hand was introduced into the uterine cavity and 1 placenta with 2 sacs was removed, and although there was no marked bleeding at this time, but because of continued relaxation of the uterus, iodoform packing was introduced into the uterine cavity and vagina.

While under the anesthetic at the time of rupturing the membranes, a specimen of venous blood was taken: The blood Wassermann was later reported negative and the blood sugar 83 mg. Examination of the amniotic fluid showed a specific gravity of 1.002, no sugar, and the cell count was 135 leucocytes per cubic mm.

Fetus A, female, was 28 cm. in length and weighed 17 ounces; fetus B, also female, was 16 cm. long and weighed 8 ounces; neither fetus was macerated though both were stillborn.

The smaller fetus was within the amniotic sac containing the excessive liquor amnii. The single placenta with two sacs appeared normal grossly but unfortunately, microscopic study of the placenta and autopsies of the babies were not done.

The patient's convalescence was uneventful and afebrile, the vaginal and uterine packing being removed twenty-two hours after delivery. She was discharged from the hospital on the 14th day in excellent condition and feeling well. Prior to discharge a chest x-ray was done which reported nothing to suggest tuberculous infiltration and the heart shadow appeared normal.

The follow-up examination made on January 5, 1932 (two months after delivery) found the patient in splendid general condition. The abdominal wall was lax and

showed marked striations. The pelvic floor was slightly relaxed; the uterus was in normal anterior position; the adnexa were normal, and the cervix showed bilateral lacerations without erosion.

215 EAST SEVENTY-SECOND STREET.   *(For discussion, see page 784.)*

REPORT OF A CASE OF SIX MONTHS' UNRUPTURED ISTHMIAL TUBAL PREGNANCY

HERSCHEL HEINZ, M.D., NEW BEDFORD, MASS.

(From the Obstetrical Service, St. Luke's Hospital)

A PREGNANCY actively developing for about six months, without bleeding or rupture, in an ovisac consisting solely of a markedly hypertrophied fallopian tube is an unusual occurrence. Cases partly analogous in one respect or another are to be found in the literature but none exactly comparable to this one, for which reason I report it in some detail.

The patient, a French woman of twenty-seven, was admitted to the obstetric service of St. Luke's Hospital on the fifth of September, 1931.

Her chief complaint was of intermittent pain of one month's duration, the pain being referable to the lower abdomen.

The present illness began with the cessation of menses on March 11, 1931. Believing herself to be pregnant, the patient consulted her family physician for prenatal care. For four months nothing unusual was noted by either the patient or her physician. After this period the patient remarked upon the absence of any signs of fetal life. Continued observation at no time revealed fetal movements or fetal heart sounds. The growth, however, of what was supposed to be the pregnant uterus was perfectly normal and consistent with a normally progressing pregnancy.

For a month before hospital entry the patient complained of intermittent lower abdominal pain at times accompanied by nausea and vomiting and occasionally of sufficient severity as to require the administration of morphia. The examination of the abdomen by the family physician at the time of these attacks disclosed no apparent intra-abdominal pathology. Two weeks before entry the blood pressure began to rise. During the forty-eight hours previous to admission the systolic pressure rose from 160 to 208. The blood pressure in two previous pregnancies had never been over 120. The present illness was unaccompanied by fever, bowel or urinary disturbance, or any evidence of bleeding, either external or internal.

The past history was essentially negative. The patient had had two normal pregnancies terminating by low forceps. The menses previous to the present illness had been regular, of the twenty-eight day type. The flow was moderate in amount, of normal character, and of four to five days' duration. The patient's last period was normal in every respect. There was no history of dysmenorrhea, intermenstrual bleeding or vaginal discharge. No history of venereal disease could be obtained from either the patient or her husband.

The patient was a fairly well developed and nourished woman apparently in moderate pain. The color was good. Temperature 99.4° F., pulse 88, and respirations 20. The blood pressure was 208 over 134.

The general physical examination was negative except for the presence of marked dental caries. The breasts were full and somewhat sensitive, consistent with the mammary enlargement of pregnancy.

Abdominal examination revealed the presence of a smoothly globular, freely movable mass, reaching to, or a little above the umbilicus with the patient in a reclining position. This mass was firm and tense, resembling in feel the uterus in a case of ablatio placentae. It was somewhat tender to pressure. During the examination the

patient complained of continuous lower abdominal pain. No contractions or relaxations of the mass could be observed. The abdominal examination was otherwise without significance.

Vaginal examination showed a slightly violet-tinged mucous membrane. The cervix was in normal position, small, and much firmer than one would expect in a multiparous woman. Hegar's sign was absent. The os was about one-half cm. in diameter. Movements of the mass were reflected only slightly in the cervix, the two apparently not intimately connected. To the right of the midline a smaller mass could vaguely be felt by bimanual palpation and this seemed to be more closely associated with the cervix. The examination was otherwise negative.

The urine showed a very large trace of albumin with an occasional granular cast. A roentgenogram was reported negative for pregnancy but later was stated to have been incorrectly exposed.
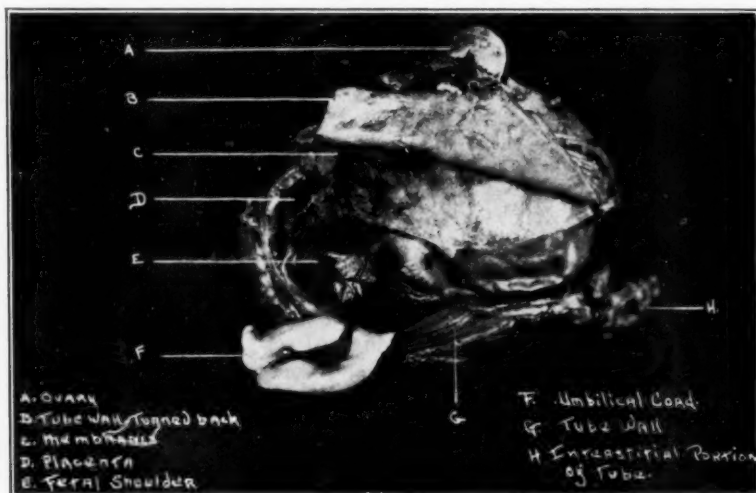
Fig. 1

The diagnosis presented obvious difficulties. The possibility of a rudimentary horn pregnancy was considered. In view of the pain, rising blood pressure, and the character of the mass it was considered advisable to do an immediate laparotomy.

The operation was performed under novocaine spinal anesthesia, the abdomen being opened by a midline incision from pubis to umbilicus. On opening the peritoneal cavity the mass was found to be a freely movable tumor lying approximately in the midline. It had the appearance of a normal six months' pregnant uterus. With good exposure, however, it was readily seen that the mass was tubal in origin. The uterine attachment of the left tube was hypertrophied and about two centimeters in diameter gradually swelling to form a tumor somewhat larger than a good sized grapefruit. The left broad ligament was proportionately widened and full of dilated, tortuous blood vessels. The ampullary end of the left tube and the left ovary arose from the posterior surface of the tumor and were intimately attached thereto. The sigmoid was loosely adherent over a small area on the posterior surface of the tubal mass. There was no blood or exudate in the pelvis nor any evidence of previous bleeding.

The uterus was displaced slightly to the right of the midline and was enlarged approximately to the size of a two months' pregnancy. The right tube and ovary were normal and free.

The sigmoid was easily dissected free of the tube. The left mesosalpinx was divided between clamps and the tube resected from the uterus by a wedge-shaped in-

cision. All bleeding and raw surfaces were then sutured with No. 2 chromic catgut, and a routine appendectomy was performed after which the abdomen was closed in layers without drainage. The patient left the operating room in excellent condition. Her convalescence was smooth and uneventful, the maximum temperature being 100° F., on two occasions only. Twenty-four hours after operation the blood pressure was 140 over 110, and on September 18 when the patient left the hospital, it had reached a normal of 122/84. The urine examination on discharge was negative.

The excised tubal mass was opened by a short incision, with an immediate gush of clear amniotic fluid and the extrusion of an umbilical cord about three-quarters of a centimeter in diameter. (Fig. 1.) The wall of the tube in its central portion was one centimeter in thickness. The specimen was placed immediately in ''Museum'' fluid, pending examination by our pathologist. This caused some shrinking so that measurements made at a later date are somewhat smaller than those made at the time of operation.

The fetus was well preserved and although the fetal heart was not beating it was quite evident that life had been present up to within a short time of the operation. The embryo, a female, was perfectly developed and weighed 375 grams. Its crown-rump length was 16 centimeters, crown-heel length 25.5 centimeters.

The measurements and the weight of the fetus show its development to be between five and six months which checks well with the period of pregnancy as calculated from the date of the last menstrual period. It is to be assumed that the growth of the fetus must necessarily have been retarded by the restricted space in which it was developing.

An x-ray of the tubal mass taken after its removal from the abdomen showed the skeletal structure of the fetus, the development being normal for its apparent age.

The examination of the specimen was made by our pathologist, Dr. Isabel M. Wason, whose report is as follows:

Gross.—The specimen consisted of a large round tubal mass and an ovary. The mass, which measured 12 by 10 by 9 cm., was in the middle portion of the tube with the short tubal pedicle on one side and on the other approximately 2 cm. of tube ending in a fimbriated extremity. This mass had been opened revealing a fetus, cord, and placenta which was still attached to the wall. Membrane could be peeled away from the inner wall. Muscle composed the greater portion of the wall which was 6 to 8 mm. thick.

The fetus has already been described.

The ovary measured 3 by 2 by 1.5 cm. It was firm and contained a corpus luteum which comprised about half its mass.

Microscopic.—Tube: Sections taken from the pedicle showed the structure of the proximal portion of the fallopian tube, with empty lumen and broad folds covered by intact epithelium. In the distal end the folds were thin with free tips and were covered by well-preserved epithelium. Only a few scattered small monocytes appeared in the folds and walls. The outer walls of the mass in the central portion consisted of hypertrophied smooth muscle fibers. The inner wall showed sheets of syncytial cells and chorionic villae. Part of the decidua was necrotic and a few polynuclear and mononuclear cells invaded the wall beneath. The chorionic villae were covered by a single layer of epithelium.

The ovary contained a well-developed corpus luteum. No undeveloped follicles were seen in the sections but there were a number of hyaline scars.

DISCUSSION

An unusual case of ectopic pregnancy is presented.

Certain interesting features of this case which manifest themselves are:

First, the degree of hypertrophy undergone by the tube. It is remarkable that this could have occurred in a structure not ordinarily thought of as a muscular or very distensible organ.

Second, the absence of involvement of any pelvic structures other than the tube in the formation of the ovisac.

Third, the apparently normal development of the fetus which was probably not arrested until shortly before the patient entered the hospital. The amount of sub-cutaneous tissue was somewhat less than is normal for a corresponding period of intra-uterine development but this is to be expected from the limited space occupied by the growing fetus.

Fourth, the rise of blood pressure and beginning kidney pathology without sub-jective symptoms, both responding promptly to the termination of the pregnancy without specific treatment. One may conjecture that this manifestation of toxemia is analogous to that seen in cases of multiple pregnancy, polyhydramnios, and allied conditions.

7 NORTH ORCHARD STREET.

CANCER OF THE VULVA IN YOUNG WOMEN*

HYMAN STRAUSS, M.D., BROOKLYN, N. Y.

(Assistant Visiting Surgeon, Brooklyn Cancer Institute)

CANCER of the vulva is relatively rare in young women. The earliest case re-ported was found to be that of a young girl of fourteen years, by Kinoshita, and a woman twenty years of age, by Ossing.†

Taussig reports cases of vulvar carcinoma in two women, one twenty-seven and the other thirty-three years of age. The Mayo clinic has reported no case of a pa-tient under thirty years of age.

CASE 1.—B. K., white, aged twenty-two, born in U. S. A., married, but never pregnant. Patient was in very good health until the onset of present illness in September, 1930. At this time she noted an inflammation of the right labium majus, for which she used several ointments. The lesion ulcerated in a short time, and she consulted a doctor who advised continuation of the salves. As the inguinal nodes on the right side became involved, she developed pain in right side and groin. Two months later, the local lesion was cauterized. After a few weeks the lesion recur-red. A blood Wassermann at this time proved negative. No loss of weight occurred. The patient entered a local hospital where a biopsy was taken. The pathologist's report of this was:

Microscopic examination showed the normal tissues to be largely replaced by a squamous cell epithelioma composed of nests, columns, and more diffuse masses of pavement epithelium supported by relatively sparse fibrous stroma which was well vascularized and densely infiltrated with inflammatory cells, most of which were of the lymphocytic variety. The neoplastic epithelium in places was well differentiated and showed cornification and pearl formation. In other places the cells were more or less anaplastic and many of them exhibited mitotic figures. In several areas, the tumor was seen to arise from the pavement epithelium covering the surface of the vulva. In other areas, the surface showed necrosis or ulceration.

Diagnosis.—Squamous cell epithelioma of the vulva.

The local lesion was coagulated with the high frequency current. The inguinal glands were not treated. On February 21, 1931, she was admitted to the Brooklyn Cancer Institute; she weighed 103 pounds. She had a slight leucorrhea, no urologic symptoms, her menstrual history was negative. The internal genitalia were nega-

---

tive. There was a slight leucorrhea which could not be explained by any physical findings. The right labium majus and minus were markedly hypertrophied. The superficial epithelium was desquamated. In the center of this area of desquamation, and definitely away from Bartholin's duct, there was an ulceration 2 cm. in diameter. The edges of the ulcer were indurated, elevated and rolled. There was a marked secondary infection which caused the lesion to be exquisitely tender. The opposite labia were normal in all respects. There was present a moderate serosanguinous discharge. The inguinal glands on the right were enlarged but not ulcerated. The glands in the left groin were barely palpable. There was slight amount of pain in the right thigh.

X-rays showed no metastasis in lungs or bony pelvis. Blood count showed hemoglobin 70 per cent, type 2, R.B.C. 2,490,000 normal cells, W.B.C. 9,600, Polymorphonuclears 80 per cent. Treatment was begun with deep x-ray therapy to the pelvis. The high voltage x-ray cycle consisted of the following factors: 5 ports, 2 anterior, 2 posterior, 1 perineal, size 20 by 20 cm., 50 cm. distance, 180 kv., 4 ma. Filtration, ½ mm. copper and 1 mm. aluminum. 215 R units to each port. This was repeated every second day until six treatments were given. The average patient is about 8 inches thick. Over one-half the radiation intensity therefore, reached the mid-pelvis, which received 62½ per cent of a S.E.D. at each sitting.

On March 25, under avertin anesthesia, 15 platinum needles were implanted around the vulvar lesion. The following factors were involved: Applicator, 15 platinum needles 35 mm. long; content, 2½ mc. radon each; filtration, 0.5 mm. platinum; duration, five days and four hours; dosage, 3000 mc. hours, Ten days later, another x-ray cycle was administered. The right inguinal glands became infected and fluctuant, and were incised and drained. The area of ulceration on the vulva subsided slightly. The patient's general condition improved to a slight extent. It was decided to radiate the inguinal gland, as we felt that the infection was well walled off. A tube of radon was applied to this area. The following factors were involved: Applicator, 1 platinum tube; contents, 10 mc. radon; filtration, 1 mm. platinum; duration, four days and five hours; dosage, 700 mc. hours. The glands in the left groin enlarged, and gradually became definitely involved in the spreading process.

Two months later, the patient was discharged to a convalescent home, and later received a repetition of the x-ray therapy. The disease, however, progressed, and the patient reentered the hospital, at which time examination showed one lymph node in the right groin the size of an egg, red, tense, and tender. The other nodes on both sides had ulcerated, the vulvar lesion had extended to the mons veneris, and ulcerated the adjacent tissue and spread to the left labia. The blood study showed a moderate anemia. X-ray of lung and bony pelvis still negative. Patient became extremely weak and emaciated. She had a profuse hemorrhage from the right inguinal lesion which was controlled by packing. At no time did the patient have edema or varicosities of the legs. The suprapubic ulceration extended to the bladder which was exposed, as was the rectus muscle and the pubic bone. Both groins broke down, and ulcerated very extensively; exposing the fascia lata and the external iliac vessels. Her condition became progressively worse, and on August 5, 1931, she died. No autopsy was obtained.

CASE 2.—F. R., a negress, aged twenty-nine, widowed, and mother of one child. General condition good until present illness. Definite history of syphilis.

About July, 1929, the present illness started as an itch of the vulva which was treated with blue ointment, lysol locally, and lysol douching. A pimple developed which she squeezed. At this time she was told that her blood was bad, but she neglected to take treatment for a year. She entered a local hospital in June, 1930, complaining of a hard mass involving both labia majora and infiltrating the tissues, extending into the vagina. The clitoris was also involved. There was no involvement of the inguinal lymph glands. Spinal Wassermann was negative. Biopsy was taken and reported as follows:

Microscopic Examination.—The section showed mucous membrane and underlying submucosa. There was a marked hyperplasia of the stratified squamous epithelial cells of the mucosa and the basal cells showed marked pigmentation by melanin. Invading the submucosa in rather irregular islands and torturous columns were found epithelial cells derived evidently from the overlying mucosa. The invasion was rather disorderly in character and the differentiation was fairly well marked. The remainder of the submucosa was densely invaded by polyblasts.

Diagnosis.—Epidermoid carcinoma.

This patient received six injections of 0.6 neoarsphenamine and eight intramuscular injections of 1 c.c. of bismogenol, Wassermann was 2 plus. She was referred to the Brooklyn Cancer Institute where she received a course of high voltage x-rays to the pelvis, consisting of the following factors: 5 ports, 2 anterior, 2 posterior; 1 perineal, size 20 by 20 cm.; 50 cm. distance; 180 kv.; 4 ma; filtration, ½ mm. copper and 1 mm. aluminum; 215 R units to each port. This was repeated every second day until six treatments were given. The average patient is about 8 inches thick. Over one-half the radiation intensity, therefore, reached the midpelvis, which received 62½ per cent of a S.E.D. at each sitting.

On September 15, 1930, she was hospitalized; she weighed 99 pounds. She had no urologic symptoms. Spinal fluid gave a negative Wassermann, while blood was three-plus. Blood chemistry normal. Blood count, red blood cells 4,180,000, white blood cells 4,000, Polymorphonuclears 70 per cent, hemoglobin 60 per cent. Vaginal examination showed vagina, cervix, uterus, and adnexa normal. There was marked ulceration from the symphysis pubis extending into the vagina. The ulcerated area was about one inch wide, exposing the pubic bones. The edges were ragged and bleeding, the inguinal glands were enlarged.

While in the hospital, she received a radium treatment of 3000 mch. distributed in 18 tubes of 10 mc. radon each, placed on a wax mold 1 cm. distance from the lesion, over a period of eighteen hours. Each tube was filtered by 1 mm. of platinum. The following week, patient received an additional 3000 mch. The factors involved were eighteen needles of platinum, 35 mm. long, and 5 mm. thick containing 2 mc. radon each, and these were placed by puncture around the growing margin for five days and eight hours.

On September 28, 1930, the patient left the hospital against advice. On January 17, she was again admitted to the hospital where she was originally treated. Her general condition was much worse. Her body was mere skin and bones, and she had a general glandular enlargement. The interne described the lesion as a "large ulcerated area about the vulva, clitoris, and inguinal regions, from which a horrible stench issues forth." Two blood Wassermann tests proved negative. In spite of local treatment with Carrell-Dakin solution, and Blaud's pills by mouth, she became much worse.

Again she was transferred by ambulance to the Brooklyn Cancer Institute on July 24, 1931. Her admission blood study revealed negative Wassermann, hemoglobin 20 per cent, R.B.C. 1,620,000, with marked anisocytosis and poikocytosis. The W.B.C. were 3,970 with 73 per cent polymorphonuclears.

X-ray at this time showed destruction of portions of the pubic bones and ischial rami. She complained of severe vulvar and lower abdominal pain with intense burning of the genitalia. The pubic bone was exposed, the bladder wall was visible, the mons veneris was gone, and all the landmarks were gradually lost. The area of destruction extended up the anterior abdominal wall, midway between the pubis and the umbilicus, and posteriorly as far as the anal orifice. This entire lesion was fungating, sloughing, bleeding, discharging, and foul smelling. The legs never developed edema or varicosities. The cachexia increased, she became irrational, and on August 17, 1931, she died. Autopsy permission was refused.

755 Ocean Avenue.

Society Transactions

The following papers were presented:

The Present Position of Version and Extraction, Drs. Joseph L. Baer, Ralph A. Reis, and James J. Lutz, Chicago, Ill. (See page 599, October issue.)

DISCUSSION

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—In a survey made in 1931, by a Philadelphia committee on maternal mortality in that city, out of 33,000 deliveries, 23,000 occurred in 53 hospitals during the year. Among these were 359 versions and extractions, an incidence of 1.5 per cent, which is twice as high as that given by Dr. Baer. Version and extraction is therefore being used to a considerable degree in Philadelphia. Out of 23,000 women, confined in hospitals, 4,800 were delivered by forceps, of which 187 were high operations, an incidence of 0.37 per cent. There were 576 cesarean sections, an incidence of 2.6 per cent. High forceps would therefore seem to be almost a negligible operation in Philadelphia. Version and extraction still retain a fair place in operative obstetrics. I believe that the mortality following version was much lower proportionately than from high forceps and very definitely lower than it was following the 576 cesarean sections.

DR. ALFRED C. BECK, BROOKLYN, N. Y.—In our clinic in Brooklyn we follow very much the outline recommended by Dr. Baer. We have found, however, an additional aid in the use of the abdominal binder during the second stage. Since we have been using this routinely, the need for any of these three procedures has been very greatly diminished. We also teach our students to give more regard to the first stage of labor, so that when the patient reaches the second stage she will be strong enough to make the binder of value.

DR. J. M. BERGLAND, BALTIMORE, MD.—At the Johns Hopkins Hospital during the past year we have done very few versions and extractions and, I am glad to say, extremely few high forceps. We appreciate the difficulties of these procedures, and as opportunities for doing versions and extractions are becoming fewer, we feel that our skill in doing this operation in a satisfactory way is diminishing. However I believe that probably we are not doing as many versions and extractions as we should do. We follow the technic of Potter as nearly as possible, and I believe that his suggestions for the performance of the actual operation are valuable; on the other hand, I am sure that one of the most important things done in our Clinic during the last year has been the liberalization of the indications for cesarean section.

DR. EDMUND B. PIPER, PHILADELPHIA, PA.—I would like to make one possible criticism regarding the question of terminology and the word "elective." In our teaching at the University we use three indications for podalic version; first, the routine cases; second, elective; and third, emergencies. We only use the term "emergency version" where it is done in the presence of failing fetal heart sounds, but we use elective version when there is a choice between version and forceps.

I believe that podalic version is one of the most difficult, if not the most difficult, operation in obstetrics.

DR. BAER (closing).—Dr. Williams emphasized a point, namely that we had not given version and extraction its proper place in these last five years. His figures are about what should be and which we are now hoping to attain.

Dr. Beck's comment about the value of the abdominal binder in the second stage of labor is a highly important one. If the patient is a multipara with a pendulous, grossly relaxed abdomen, I regard the binder as definitely desirable. I am not yet convinced that for the normally sound abdominal wall the binder is anything more than perhaps a handicap to proper observation of the heart tones during the second stage. So, except where specifically indicated, we do not use it.

With reference to my misuse of the word "elective," what I had in mind, of course, was the "routine" or Potter type of version and extraction and Dr. Piper's comment was entirely justifiable. Version and extraction may be routine, elective, or emergency.

I cannot feel that version and extraction should be characterized as essentially a difficult operation. I do believe we should emphasize that the trained obstetrician should know how to do version and extraction. If he possessed that knowledge and skill, then I regard it as a comparatively simple procedure in the suitably selected patient, and I rather deprecate the position that version and extraction should be labeled by this Society as one of the most difficult of operations.

A New Axis-Traction Forceps, Dr. Edmund B. Piper, Philadelphia, Pa.
(See page 625, October issue.)

DISCUSSION

DR. NORRIS W. VAUX, PHILADELPHIA, PA.—First, a word of warning about Dr. Piper's forceps, the model he has just now presented. It is a very dangerous forceps because the force of the axis-tractor is tremendous if not applied properly. With care, this instrument needs very little traction, and if too much force is applied, there may be very extensive internal and external injuries, accompanied by profuse hemorrhage, and from lacerations occurring in the improper use of any type of forceps. The warning is not to pull too vigorously but rather very cautiously throughout the operation. This instrument is used quite routinely in our service. It also can be applied to the after-coming head quite as simply as the forceps previously devised by Dr. Piper for this purpose.

DR. WILLIAM E. CALDWELL, NEW YORK CITY.—We have used his forceps at the Sloane Hospital for Women for several months. It has given very satisfactory results, making all types of operation simpler.

The instrument is well made, the fenestra nicely cushioned; there is a considerable spring to the blades which prevents excessive pressure although holding the head nicely; the curve of the shank gives excellent axis-traction. The forceps resemble greatly the Lusk modification of Tarnier's original forceps. Although the axis-traction principle was developed for use when the head was high in the pelvis, especially for high forceps, it is the proper maneuver anywhere in the pelvis, even for low forceps.

In rotating the head we agree with Bill that it should be rotated in the planes of the greatest diameter, preferably by hand, if necessary with a solid blade forceps or the Barton instrument. Dr. Piper's forceps have to be handled with great care and skill when used as rotators.

DR. JOSEPH B. DeLEE, CHICAGO, ILL.—I would like to condemn all axis-traction forceps, not particularly Dr. Piper's or Tarnier's, on the grounds that the axis-traction forceps is not artistic. One simply applies a big heavy pair of tongs

and then pulls and the soft parts and the pelvis force the direction in which the head has to move. As the last speaker has shown, the axis-traction forceps cannot be used for rotation.

Dr. Piper stated that I preach the use of single forceps for all work. That is true for the general practitioner, but there are two forceps on the market which are useful in certain conditions, in the hands of the expert, the Kielland and Barton's forceps. I have used the latter simply for the purpose of pulling the head into the inlet when the head lies high in the transverse diameter. For that purpose I think it is the best instrument that we possess today. After the head has been brought down into the pelvis the Barton forceps is removed and the rest of the operation completed with manual rotation, aided if needed by the Simpson forceps. I think the use of high forceps should be limited in favor of version. In difficult cases where the axis-traction forceps would be used, the delivery could be probably better effected by version and extraction.

I can imagine a case where the head is packed into the pelvis and where brute force applied with the axis-traction instrument would be necessary. Dr. Rubowitz has invented the term "precraniotomy forceps" and I think that is a good name for those high forceps operations done in the tender hope of getting a live baby when the only alternative is craniotomy. Craniotomy is a rare operation and getting less necessary all the time. I would call attention to the fact that the obstetrician still has a pair of hands and has eyes at the end of his fingers, and that aided by a study of the mechanism of labor he can use the Simpson forceps in practically all of the cases where it is necessary to make an instrumental delivery.

DR. WILLIAM B. HENDRY, Toronto, Canada.—In Toronto we have been confused by the profusion of the types of forceps on the market to such an extent that one of the junior members of our staff has undertaken to make a forceps which would combine the good qualities and have none of the defects of all the forceps. We are inclined to think that probably he has succeeded in this. The principle of his forceps depends upon being able to split a universal joint, which enables one, without removing the forceps after it is once applied, to perform the operation of bringing the head into the pelvis, doing a rotation and also an extraction.

DR. PIPER (closing).—Just to reiterate the last sentence of my paper, I made those forceps to suit myself, and it does not interest me particularly whether anybody else likes them or not.

I agree with Dr. Caldwell that rotation of a head with any instrument is a difficult and dangerous procedure.

Dr. DeLee said that no axis-traction forceps should be used. He does not do high forceps very often, which might explain the rather high incidence of elective cesarean section in that clinic.

I wish I were able to do without an axis-traction forceps. I wish I could deliver a baby as Dr. DeLee does, but I cannot, and I want to get the forceps that makes it as easy as possible without injuring the baby and the mother, which I can do readily with these forceps I have exhibited.

Twelve Years' Experience With Uterotubal Insufflation: Diagnostic and Therapeutic, Dr. I. C. Rubin, New York City. (See page 561, October issue.)

DISCUSSION

DR. NORMAN F. MILLER, Ann Arbor, Mich.—To maintain a permanent place in medical practice every diagnostic test must meet certain qualifications. It must be safe; it must give sufficient information to warrant its use; and it should not be technically difficult.

Dr. Rubin has shown that if proper precautions are taken his test is practically without morbidity. My own observation and experience would tend to substantiate this. No serious complication occurred in over 400 tubal insufflations at the University of Michigan. Only in one case have I seen high fever and signs of pelvic inflammation following the test. The indications, requirements, and contraindications laid down by Dr. Rubin are based on long experience and the analysis of abundant clinical data. They should serve as standards, and any competent physician willing to observe these rules may use the test with safety.

Does the test give sufficient information to warrant its routine use? The answer is obvious. If it gave only half as much information I would still consider it a necessary procedure in every study of sterility. Indeed, it is no longer simply a tubal patency test because in its present highly developed form it is possible to obtain much additional information. For instance, spasm, partial, or complete stricture of the tube and its probable location may be determined by tubal insufflation with kymographic attachment. As a diagnostic procedure it is not only safe but indispensable in the study of sterility.

I must confess, however, that my preference lies in the use of opaque substances injected under controlling fluoroscopic examination. By this method we learn just as much concerning tubal patency, and we obtain a better idea as to the character and location of tubal stricture or obstruction. If plates are taken at the time of injection and again within twenty-four hours a more desirable permanent record of the condition of the tubes is obtained. Furthermore, I have greater confidence in the findings demonstrated by this method. Dr. Rubin reported nearly 7 per cent morbidity following the use of opaque substances. This seems very high. As yet, I have seen no untoward results from the employment of oil, but I perhaps shall go back to CO_2 after reading Dr. Rubin's forthcoming monograph on the use of opaque substances.

So far as the third qualification is concerned the technical difficulties of the test are certainly no obstacle to its use. In this respect it is superior to the injection of opaque materials. The use of x-ray often means inconvenience as well as added expense, both of which are important drawbacks to oil injection as a routine procedure.

The therapeutic value of tubal insufflation is as significant as it is spectacular.

The fact that 66.6 per cent of 57 dysmenorrhea patients were relieved following the test certainly warrants further study. To my knowledge few remedies or therapeutic measures can surpass this record.

Just how much time may lapse between the test and subsequent pregnancy in order to justify attributing the result to the test is perhaps open to discussion. It seems to me, however, that Dr. Rubin is very fair and conservative when he states that "pregnancy must follow within a month or at least two months after insufflation."

That uterotubal tonicity is increased during the tenth to the sixteenth day of the menstrual cycle and decreased in functional amenorrhea of young women, is in my opinion, a most interesting observation. This would appear to support the views on tubal propulsion of the ovum.

I should like to ask Dr. Rubin what significance he attaches to the fact that 60.46 per cent of tubal obstructions followed appendicitis? Even though the right tube be involved one would not expect so many closures on the left side.

DR. N. SPROAT HEANEY, Chicago, Ill.—An analysis of 90 cases, in 1931, of pure sterility cases, i. e., cases which presented themselves for this chief reason, showed 60 per cent of the cases had absolutely normal tubes, 15 per cent were patent with some slowness and 24 per cent were absolutely closed. The patency test is of utmost importance when operating upon fibroids of the uterus in young women. If before the operation the tubes are found open, then the patient may

be told that there is a possibility of a myomectomy being done. If the tubes are closed, however, then a myomectomy would not be advisable for such an operation is only to be done to conserve childbearing, the chances of the recurrence of fibroids being great enough to forbid its use on the sterile woman.

DR. CHARLES C. NORRIS, PHILADELPHIA, PA.—A use for the Rubin test which was not mentioned by the essayist is occasionally found in those patients in whom it is desirable to employ intrauterine irradiation with radium for benign hemorrhages and in whom there is some question as to the condition of the tubes. Occasionally patients are encountered in whom palpation yields somewhat doubtful results and in these insufflation offers a valuable method of determining the condition of the tubes, for when these are not patent, radium is usually contraindicated.

DR. NATHAN SEARS, SYRACUSE, N. Y.—I would like to ask Dr. Rubin whether he considers it necessary to use x-ray as a routine or whether he can depend on the fluctuation of the monometer and the subsequent shoulder pain?

DR. RUBIN (closing).—In answer to Dr. Miller's question, about 60 per cent closure of tubes were found in appendicitis cases. Not infrequently, even in mild cases of appendicitis, there is a serous exudate in the pelvis, that results in cobweb adhesions implicating the left tube also. Where abscess formation takes place it also occupies the left side as well as the right.

Dr. Heaney was quite right about fibroids and tubal patency. I am accustomed to examine the tubes for patency in women still in the reproductive period of life who have fibroids and want to know whether a myomectomy can be done.

In reply to Dr. Sears, I have been in the habit of using the fluoroscope as a routine. I am still interested in the scientific check-up of all the data involved in the test; but the fluoroscope is not absolutely necessary. I think the kymograph and the shoulder pains give you all the necessary information. Where the kymograph is not available one can train himself to note the fluctuations of the mercury column. After a little practice one becomes adept at doing that and it is helpful.

The kymograph enables us not only to tell whether the tubes are patent but the degree of patency, i. e., whether they are normally patent, and if not normal, what kind of stenosis is present, and also whether there are peritubal adhesions or utero-tubal spasm. In the vast majority of cases it is possible to locate the site of obstruction. The decision for or against operation to open the tubes is thus rendered possible and in this respect abdominal auscultation and careful notation of the sensory reactions during the insufflation examinations are important.

Another interesting thing to mention, as to the therapeutic action of insufflation, is that it was employed more than once in 247 of the 298 cases that became pregnant and in 27 per cent pregnancy followed within one month after the insufflation. That is a fair criterion if one wants to judge of its therapeutic value.

The Prophylactic Treatment of Thyroid Dysfunction and the Importance of Basal Metabolism Studies in Obstetrics and Gynecology, Dr. Carl Henry Davis, Milwaukee, Wis. (See page 607, October issue.)

DISCUSSION

DR. WILLIAM C. DANFORTH, EVANSTON, ILL.—The use of thyroid in a good many obstetric and gynecologic cases is valuable and especially in hypothyroid conditions.

I believe there is a class of women who are more than normally inclined to abort who in the presence of a low basal rate are helped by the administrations of thyroid.

As to routine administration of iodine in all pregnant women, I would not agree. I have at the moment two women under my care who have been greatly benefited

by the administration of small doses of iodine but I would be rather hesitant about using iodine generally. I think the routine use of iodine may be of greater necessity in some regions of the world than in others and that should be taken into consideration. I have found that a very useful way of giving iodine is to use a saturated solution of sodium iodide. Patients seem to tolerate it over a considerable period of time. When the patient also has a moderate anemia, the iodide of iron has been found a very useful preparation.

DR. EDWARD A. SCHUMANN, PHILADELPHIA, PA.—I have been impressed by the importance of Dr. Davis' paper as applied to certain sections of the country and as opposed, if I may say so, to its lack of importance as regards other regions. Of course, as you all know, the entire area from the St. Lawrence Basin through the Great Lakes region, involving Wisconsin, Minnesota and that part of the West, was during the three glacial epochs under glaciers, and there were no iodine bearing flora or fauna developed in that region. On the Atlantic seaboard our incidence of goiter in infants is extremely low and I fail to recall a single case of congenital, rapidly developing goiter in my experience. Therefore, the necessity for routine stabilization of the thyroid is unimportant in the region from which I come.

I would disagree slightly with Dr. Davis in minimizing the danger of routine iodine administration. It is well known that about 8 per cent of all women between the ages of twenty and forty years possess possibly occult adenomas of the thyroid and while the routine administration of iodine may stabilize the thyroid output, it unquestionably stimulates adenomatous growth, and there have been a number of cases recorded of rapid development of the adenomas after the routine administration of iodine.

With regard to the use of thyroid extract, particularly in cases of sterility of unknown origin, I believe that this is a most important measure and I would point out the fact that apparently normal variations of the basal metabolism rate, minus 2 or 3 or 4 which fall within the normal reading, sometimes show the greatest clinical success upon the administration of fairly large doses of thyroid for a short period. I have had several instances of the empirical administration of thyroid in large doses with startling results.

DR. CAREY CULBERTSON, CHICAGO, ILL.—There is no condition in which the metabolic rate is more important to study than one to which Dr. Davis merely referred, that is, the climacteric. It was shown years ago that there is an instability of the blood pressure during this time of life, and we know that the basal metabolic rate is also disturbed. If that is so, it is difficult indeed during the climacteric years to evaluate accurately what is going on in individuals, whether they are developing hypo- or hyperthyroidism, and whether that condition is purely functional or is organic. I make these observations, because I have seen a number of patients in whom thyroid operations have been undertaken during the climacteric years, without any appreciable benefit whatever. I think this is a time when metabolism studies should be frequent and as accurate as possible. Too often the results obtained from such observations have been without avail, without any diminution in the symptomatology. We can group our climacteric cases into the hypo- and hypertensive types. The hypertensive cases have vasomotor disturbance and the hypotensive cases have symptoms suggesting hypothyroidism. The difficulty is in estimating how much of this condition is functional and how much is not. My experience has been that in the climacteric years the women will not be benefited by surgical therapy as the disturbance is usually transitory at the most.

DR. KARL M. WILSON, ROCHESTER, N. Y.—This problem which Dr. Davis presents is very important to us who live in the Great Lakes region. I would like to mention a prophylactic measure used in our community. Several times a year the whole water supply is iodinized with salts and that means, of course, that the whole

community gets the benefit from it whether they want it or not. Of course, that is no substitute for the careful study and observation of the individual patient, but I would like to point out that since that has been done in the past few years the incidence of congenital goiter has gone almost to the vanishing point, and goiter in school children has been reduced to about two-thirds of the usual number. Therefore, it is quite worth while. However, that would not be adequate treatment in a woman who shows a definite insufficiency.

DR. DAVIS (closing).—Fortunately Dr. Danforth is caring for a class of patients who from time to time go to the seashore. Most of his patients are traveling about more or less or get a considerable amount of seafood and therefore getting some iodine whether he gives it to them or not.

Dr. Schumann must take into consideration, I believe, the individual patient because patients who have been raised in goiter areas may from time to time migrate to Philadelphia, and if so it is very probable that if he is going to save the patient with a thyroid deficiency from developing children with an abnormal thyroid he must give that patient an adequate amount of iodine. Some may need small doses of desiccated thyroid in addition.

It is perfectly true that patients who are getting iodinized salt have in this country developed hyperthyroidism and toxic adenomas. But in view of the fact that all over Michigan, where the use of iodinized salt is compelled by law, the number of operations for toxic goiter has been greatly reduced, must be accepted as evidence that the use of iodinized salt has not increased the frequency of goiter. In Switzerland toxic goiter is practically unknown. They operate for cystic goiter and tumors of the thyroid but they do not have the type of toxic goiter which we see in this country. I feel that there is more and more evidence that the nervous system is responsible for the development of toxic conditions of the thyroid, and that it is not possible in view of our present manner of living for people with thyroid gland deficiency to avoid developing hyperthyroid states from time to time.

It is important to study these conditions in relation to the menopause, as Dr. Culbertson has pointed out, but it has been possible only to consider one phase of this subject today. I have tried to bring to your attention, with the hope of serious consideration, the importance of prophylactic treatment of thyroid disease as a means of preventing conditions which are easily prevented, and also suggest that we may in this way solve some of our other problems pertaining to the glands of internal secretion.

Results With Cordotomy for Relief of Intractable Pain Due to Carcinoma of the Pelvic Organs, Dr. Francis C. Grant, Philadelphia, Pa. (By Invitation.) (See page 620, October issue.)

DISCUSSION

DR. FLOYD E. KEENE, PHILADELPHIA, PA.—Any procedure which gives promise of alleviating the sufferings of advanced carcinoma is worthy of serious consideration. Out of every 100 cases of cervical cancer the methods we employ are curative in only about 20 per cent, which means that in the remaining 80 per cent, the procedures used are at best only palliative. With the modern methods of irradiation, a large percentage of this incurable group will obtain at least temporary respite but in others, the response will be unsatisfactory, the pain will not be influenced and other measures must be used for relief.

The results which Dr. Grant has reported in his 25 cases of malignancy demonstrate beyond question of doubt the value of cordotomy. The relief from pain is usually not only complete but permanent, the procedure, when properly performed, is unattended by motor or functional disturbances and the patient's life is made

livable for the time that remains. The mortality of 16 per cent does not argue against the operation for, under such conditions, death is kind.

I am not sufficiently informed to discuss the relative merits of cordotomy as opposed to periarterial sympathectomy or excision of the presacral plexus. In a recent comprehensive review, Lorraine and Hermann reported results equal to Dr. Grant's and they assert that with the later procedures the technic is simpler, easier to acquire, that the operation is associated with no functional disturbance, and that the same operation enables one to verify the nature as well as the extent of the lesion. From the very limited experience which I have had in patients operated upon by Dr. Grant and Dr. Frazier, I believe that in a few properly selected cases, there is a definite place for these operations in the palliative treatment of extensive pelvic cancer, and that up to the present time, we have not taken advantage of the benefits which these operations may afford.

DR. RICHARD R. SMITH, Grand Rapids, Mich.—I desire to give a brief account of the corresponding experience at our University of Michigan Hospital in the Division of Neurological Surgery. This department is in charge of Dr. Max Peet who with his associates, Dr. Kahn and Dr. Allen, has done 65 cordotomies. The number corresponds almost exactly with Dr. Grant's. Of these, 21 were done for carcinoma of the uterus, 3 for carcinoma of the prostate, and 4 for carcinoma of the rectum. Since we have only one object to attain, namely the eradication of pain, we may best form our judgment of the operation on the total number rather than upon those performed alone for malignancy arising in the pelvis. The results are much the same.

In 65 patients operated upon 50 gave satisfactory results. There were 4 cases the results of which were not determined and in 11 cases the results were unsatisfactory because of morphinism, the operation having been performed at too low a level, or because pain was not permanently eradicated.

Now we must bear in mind that the one object is to eradicate pain, very imperfectly controlled by the other means at our command, and if that can be accomplished we may put up with unpleasant experiences and complications, but it is well to bear in mind in the first place that we are usually operating upon patients who are hopelessly ill with all that the situation carries with it. There is also a considerable mortality. However, it is to be noted that mortality decreases with added experience.

Urinary disturbances (retention and incontinence) have been frequent and are a complication of some importance. In Dr. Peet's cases there were at least 22 patients who had marked bladder disturbance following operation. That is not taking into consideration the number that had such bladder disturbance before operation due to the invasion of the disease. We must remember, too, that good results are not always obtained. Pain has been known to recur after many months of relief for reasons not surely determined.

The technic must be very carefully and very exactly carried out, and I think we may hope for better results when there has been more experience with the operation. Certainly the experience of Dr. Grant in having practically perfect results in the last 18 cases is significant.

DR. GRANT (closing).—I am very glad that Dr. Keene brought up the question of section of the presacral nerve and the stripping of the internal iliac arteries for relief of pain from pelvic cancer, because there have been cases reported in the literature in which this procedure has been successful. Frankly, I have had no experience whatsoever with it. The latest and apparently the most authoritative report is that by Fontaine and Hermann (*Surg. Gynec. Obst.* **54**: 133, 1932) who reports six cases of carcinoma of the pelvis, four of them having pain down the leg,

and in five of which the pain was completely relieved following this procedure. In the case in which pain was not relieved, the spread of the malignancy was so great that it was not possible to perform the operation they had in mind. The presacral tissue was infiltrated and the anatomy so distorted that the presacral nerve could not be found.

In a report that came out in 1927, Ferey (*Arch. Franco-Belge di Chir.* No. 8, 695, 1927) reported four cases of this procedure, two of which had been reported previously by him. Of the two cases previously reported one had been exceedingly successful and in the other pain had recurred. In the second two cases, the same thing happened. The patients apparently lived a sufficiently long time so that there had been regeneration of the presacral nerve.

I know little about the surgery of the pelvis but, I can imagine that in a certain percentage of these cases there would be a sufficient extension of the disease into the pelvis to make this procedure difficult. However, I think that this operation should certainly receive a trial based on the work done by different men. Certainly, in the hands of gynecologists, a presacral nerve resection would be a much easier procedure than a cordotomy. But there is the fact that out of the four cases reported by Ferey, there were two cases of recurrence.

With regard to trophic changes following cordotomy, they do occur particularly if there has been any tendency toward a trophic change before the operation was carried through. It must be remembered that many of these cases are very cachectic and if there is any breakdown of the skin prior to the operation that breakdown may become accelerated.

If cordotomy is properly performed and carried through by the technic which I suggest it is a very safe procedure in experienced hands. Dr. Smith's figures confirm this statement. We have had no difficulty of any kind in the last eighteen cases that have been done by this procedure, no motor difficulty, no retention for more than three days and no bed sores.

What do we mean by the relief of pain? We mean that patients do not require morphine and do not require any sedative or opiate to relieve their distress. A certain number of them are addicted to morphine before they come to us, so that it may be a week, ten days, or two weeks before the drug can be entirely withdrawn, but we do not consider any case as a success unless they are completely free of pain, requiring no more morphine after the operation has been performed.

Complications of Radiation Treatment in Gynecology, Dr. Frank A. Pemberton, Boston, Mass. (See page 552, October issue.)

DISCUSSION

DR. WILLIAM P. HEALY, New York City.—I would like to call attention to what we must expect to get from radiation therapy in the way of skin erythema doses in the rectal and bladder fields. We can visualize readily from observation of the skin on the abdomen what a single full erythema dose will do. As a rule it means desquamation changes in the skin. In the full four-field pelvic cycle which is used with the 200 kilo-volt machine, 15 by 15 cm. area on the skin, you get from 1 1/5 to 1 1/3 skin erythema doses in the bladder field. In the rectal field you get 1 1/3 skin erythema doses. You will sometimes see vaginal desquamation from a high voltage x-ray cycle alone without any radiation with radium whatsoever, and therefore you may see the same thing, possibly, in the bladder and rectum from x-ray radiation only.

It has been our experience in figuring out dosage that the bladder and the rectal fields in the treatment we use for cancer of the cervix will invariably get from

3 to 5 skin erythema doses, so we must expect changes to take place in those tissues as a result of this irradiation. It apparently is going to be quite out of the question for us to avoid damage to bladder and rectum with radiation therapy in treating cancer of the cervix.

A study of 50 cases of postradiation bladder complications at the Memorial Hospital shows about 2 per cent of bladder complications, primary, secondary, and tertiary. The primary occurred while the patient was receiving just the x-ray treatment alone and quickly subsided. The secondary resulted from desquamation in the bladder field, occurred in about three to six weeks after the radiation and disappeared sometimes without anything more than simple dysuria. The tertiary cases are those that usually fail to show symptoms of importance in less than one year after radiation has been given. They represent 49 of the 50 cases. There were four secondary cases, one of which cleared up and has never shown any other symptoms. The remaining 3 cases became tertiary later on.

Correct diagnosis is a most important point because further radiation may be fatal. Three of our patients had such severe hemorrhages that two of them died and the life of one was saved by doing a suprapubic cystostomy, packing the bladder, and giving three blood transfusions. We are unable to make a differential diagnosis between tumor and radiation ulcer without biopsy. None of the cases in this series gave any evidence on bimanual examination of tumefaction or fullness anterior to the cervical area.

As to the total amount of radiation that may cause the complications it has occurred in cases that received only 1000 millicurie hours of radium within the uterine cavity above the internal os, so apparently it can be a result of a very mild dose of radium.

As to the treatment of the disease, speaking only of the bladder cases, we found that they have to be treated when the symptoms are acute, with argyrol, when less acute with mercurochrome, but in the meantime the greatest relief is given by 1 per cent phosphoric acid bladder irrigations. One patient, a young woman thirty years of age, within six months after irradiation with radium and x-ray developed an acute lesion of the upper rectum and lower sigmoid. I did an exploratory celiotomy, having made a diagnosis of the lesions clinically, because of her rectal symptoms, and found that four inches of the rectum was apparently almost as gangrenous as an acutely suppurative appendix. It was swollen, red, mottled, rigid, hard, and apparently going to slough. She was a tap dancer and I felt that it would not be just to her to do a colostomy, so I placed the bowel down in the culdesac again, opened the posterior vaginal fornix, drained it above and below, and she made a perfect convalescence. It is now two years since I did that, and she is again working at her profession.

In another case Dr. Douglas Quick did a resection of the lower sigmoid two years after the patient had been treated with radium for cancer of the corpus. She had a fibrotic stenosis which caused complete obstruction, and she made a complete recovery.

DR. GEORGE GRAY WARD, NEW YORK CITY.—I have recently had the cases gone over at the Woman's Hospital to determine the cause and incidence of our complications. In the vast literature on radiotherapy there are comparatively few papers that deal specifically with a detailed analysis of complications in the different clinics. The prevailing opinion that exists, that the application of radium is an extremely simple process, and that anybody can do it is the cause, we believe, of a great deal of unnecessary suffering in the form of various complications. Regaud has stated very aptly that "it is necessary to have much experience to obtain from this method of treatment all the good that it may give without the evil that it may do."

An analysis of our material shows the following: In 558 cases of cancer of the cervix under my personal direction, there were 119 or 21.3 per cent that showed complications of some form or other varying from the minor to the severe type. In 106 cases of fundus carcinoma that we have had, 11.4 per cent developed complications. The mortality from radium therapy in all these cases was 1.1 per cent, with no mortality in Class I and Class II cases, limited to the cervix.

The types of complications: Nausea and vomiting during the application of the radium was not troublesome and was only sufficiently severe to be noted in 1 per cent of the cases. Cystitis and proctitis occurred in 4.5 per cent. Hemorrhage following the application of radium occurred in 10 per cent but there were very few of these cases that could be classed as severe hemorrhage or that required packing. Vesico- and rectovaginal fistulas occurred in 558 cases 22 times, or 4 per cent.

It was of particular interest to us to hear the reader of the paper bring out the fact that in cases that have had previous pelvic inflammatory disease, where the loops of the bowel may be adherent to the back of the uterus, there is undoubtedly considerable danger of rectovaginal or ileovaginal fistula occurring. This is in accord with our own experience. One remarkable case that I had was seen seven years ago with marked carcinoma of the cervix, Class III. She was radiated and there is no evidence of carcinoma today, although she developed a sigmoidovaginal fistula. It caused little trouble as it was small and unless the bowels were loose she did not bother about it and was able to do her work. Last autumn she developed severe pain over the sacrum, and we thought it was a bone metastasis but no evidence could be obtained of this by x-ray. Later an abscess developed which I opened and feces were discharged through the opening over the middle of the sacrum. X-ray studies showed that this connected with the original fistula via the sacrosciatic notch, which was sigmoidal and opened into the vagina. I made a temporary colostomy and sidetracked the fecal current and the patient has been apparently perfectly comfortable since. We hope that the fistula will heal, and we will then close the temporary colostomy. In cases where a supravaginal hysterectomy has been done and the stump of the cervix remains they are especially prone to damage to the bladder from irradiation and there is considerable danger of producing a fistula. In our series of 558 cases we had 40 cases which had had a previous supravaginal hysterectomy. In these cases hemorrhage occurred one and a half times more often, and fistulas were two and a half times more frequent. We are now careful to use a smaller dosage, repeated in these cases. Late obstruction of the ureter occurred in one-half of 1 per cent, and in the fundus cases we had no postradiation hemorrhages whatever.

DR. GUY L. HUNNER, Baltimore, Md.—There is nothing that disgusts me so much as the advertisements from the commercial radium concerns telling how to cure cancer with radium. If such results as reported today are obtained in the hands of the most careful men and in view of untoward results as I have seen following Dr. Burnam's use of radium, what can we expect from these men who know nothing about radium? It seems to me that our Society might consider that matter most seriously.

I have seen from 12 to 15 patients with very serious obstruction to the kidneys from the thickening in the broad ligament regions following radium treatment. Of course, no one can say how much thickening was there before the radium was used. We know how frequently in operating for cervical cancer we have to dig the ureters out of thick periureteral tissue, but these cases following radiation are among the most difficult cases of ureteral stricture that we have to deal with. They are very slow to give any degree of dilatation or of drainage but they do answer eventually and react very well to treatment.

Pelvic Endometriosis and Tubal Fimbriae, Dr. John A. Sampson, Albany, N. Y. (See page 497, October issue.)

The Morphology of the Genital Epithelia, With Special Reference to Differentiation Anomalies, Dr. Emil Novak, Baltimore, Md. (See page 635 this issue.)

DISCUSSION

DR. DeWITT B. CASLER, Baltimore, Md.—These growths are very much like carcinoma in their invasion and Dr. Sampson can trace them directly into the ovary itself. It is remarkable that these conditions have been missed up to the present time, and it is only due to Dr. Sampson's keen sense of observation that he has discovered them. I do not know whether the lesion is a common or a rare one but it probably was rare up to the present time because we have not been alert enough to find it, but I imagine that now if our attention is fixed more and more upon the fimbriated end of the tube, we will discover more of these lesions than we have heretofore.

If we can draw any clinical conclusions from these endometrial reactions, it seems to me that the one striking thing is this: We often see endometrial reactions in the incision following cesarean section. I do not believe we see them if the uterus is removed following cesarean section. We often see an endosalpingitis after a salpingectomy in the cornua of the uterus. We do not see them in the end of the tube, however, if a hysterectomy is done and the tubes are left in to conserve the blood supply, nor are we apt to see, so far as I have observed and so far as I know the literature, any reaction in the cervical stump following operation.

I believe that there must be some additional influence which has not yet been brought out. The uterus or possibly the tubes, but I believe the uterus, must exert some influence on these endometrial growths to cause them to grow in the way they do.

DR. RICHARD W. TeLINDE, Baltimore, Md.—In spite of the many discussions in this Society regarding endometriosis, its etiology and its life cycle, the subject is not yet settled, although I believe that Dr. Sampson has quite definitely settled the etiology of this one particular type. No matter what theory one may propound to explain the etiology of endometriosis, there is some stumbling block in each case. For example, it is very difficult to explain such cases as adenomyoma of the extraperitoneal part of the round ligament on a pure implantation basis, unless we assume that there is also dissemination by the lymphatics. I believe the evidence for this is very scanty. Some years ago Sampson showed us endometrium near but not actually in a lymph gland and I have never been able to find endometrial tissue actually in a lymph gland in any case of endometriosis. There seems to be a very good evidence of implantation by means of surgical instruments in the case of endometriosis in abdominal scars. In many of these cases, however, there is actually a continuity between the endometrium of the uterus and that in the scar. I have seen, however, an implant in the lower end of the scar after hysterectomy in which no continuity at all could be traced between that implant and the cervical stump or the tubes.

From the clinical point of view one point has always impressed me and that is this: Regardless of how the endometrium gets into the ovary the dissemination throughout the peritoneal cavity by rupture of the endometrial cysts seems very probable. Sampson's recent work on carcinomatosis, in which he shows a similarity between the implants of carcinoma and endometrial implants, bears out this clinical impression.

There also is evidence that in some cases serosal metaplasia actually gives rise to endometrium-like epithelium. A few years ago Dr. Whitridge Williams demonstrated cases of decidual reaction on the posterior surface of pregnant uteri, indicating that the subserosal mesenchyme has, in the presence of pregnancy, become typical decidua. The epithelium lining the "glandlike" structures, which closely resemble the glands of pregnant uteri, could be traced as continuous with the serosa of the posterior surface of the uterus. This surely suggests serosal metaplasia in the case of this ectopic decidua. Furthermore I believe there is strong evidence against the implantation theory of this ectopic decidua because of the fact that this condition frequently occurs without any adhesions. Hofbauer described 15 cases of decidua on the posterior surface of the uterus occurring in 23 uteri in Williams' laboratory. He suggests that these might have a bearing on the etiology of endometriosis. A similar picture is found in the ovary at times in the presence of pregnancy in which case the continuity of the germinal epithelium with the glandlike structures can be traced. This again suggests the possibility of the germinal epithelium being the origin of the epithelium of the endometrial glands in ovarian endometriosis.

The evidence for dissemination of menstruating endometrium throughout the pelvis via the tubes has to my mind always been rather weak. Today, however, Dr. Sampson has shown us cases in which the tubal epithelium can be traced practically into the endometrial cyst of the ovary with a gradual transition between tubal epithelium and uterine-like epithelium within the cyst. That such a transition can occur between tubal epithelium and uterine epithelium, and vice versa, there is much evidence.

DR. FREDERICK J. TAUSSIG, ST. LOUIS, MO.—The history of medicine is full of controversies in which each man has bigotedly maintained a certain point of view and held to that point of view regardless of the evidence produced on the other side. I think we owe a debt of gratitude to Dr. Sampson and Dr. Novak for attacking this problem of endometriosis in a spirit not merely of defending a particular theory, but of arriving at the general truth. The concession that Dr. Novak made some years ago as to the implantation theory and the concession that Dr. Sampson made today regarding metaplasia from fimbriated portions of the tube are evidences of this spirit.

My experience with the question of implantation dates back to 1906 in connection with the study of a few cases of ectopic decidua formation. I looked up the literature on the peculiar distribution of these islands of ectopic decidua and, perhaps without real authority, suggested the possibility that detritus from the uterus passing out from the tube, implanted upon the pelvic peritoneum, was responsible in that way for the development of these decidual-like placques.

As we look at the evidence that has been built up stone by stone, the whole subject is beginning to take form. Certain facts must be kept in mind. First of all, that the tubes are almost always open; next, that there is evidence of menstrual blood passing out through the tubes, and evidence of a peculiar distribution in the culdesac of tissue that can be only explained as implants; further, that there is, as Dr. Novak pointed out today, very definite evidence of the development of various forms of tubal, uterine, and even squamous epithelium from the celomic epithelium. Finally, there is evidence of traumatic metaplasia at certain points, as at tubal stumps and at the fimbriated ends of the tubes. I think with these facts in mind we cannot accept just one theory. First of all, we must agree that there occurs metaplasia in various portions of the genital tract without apparent cause. Secondly, there is definite evidence of implantation both in wounds and in the rupture of endometrial cysts, pointing toward the implantation theory. Third, there is the possibility of a certain activating substance passing from the tubal lumen out over the surface of the pelvic organs, and giving rise to the development

of islands of metaplasia. It seems to me that possibly this latter explanation
may be more frequent than we have heretofore thought.

DR. CAREY CULBERTSON, CHICAGO, ILL.—I wish to speak on this topic
chiefly from the point of view of the identification of the epithelial cells. We have
given this matter a good deal of study in the histologic laboratory at the University
of Chicago and feel that we have arrived at a place where the epithelial cells of the
uterine gland can be differentiated from tubular epithelial cells. There has been
some doubt occasionally expressed as to whether these hyperplastic growths, which
we call endometrial in type, are merely that in appearance by low power or actually
endometrium. A high power study of the epithelial cell of the gland shows certain
characteristics which are for the present at least fairly definite. In the first place,
the epithelial cell of the uterine gland is not granular during the ciliated phase,
or at least the cytoplasm has very few granules, whereas the tubular cell is abundant
in granules. That is fairly constant. However, the chief differentiation is that
the uterine epithelial cell produces an abundance of glycogen and the tubular
epithelial cell does not. These are points of differentiation that can be made. It
does not follow, of course, that if it can be shown that in every case the epithelium
of these apparent developments is not endometrial, that they may not be derived
according to the theory that Dr. Sampson put forth in 1921. Some of these defi-
nitely menstruate. We have all seen sections of actively menstruating epithelial
growths, always with stroma. Some of them were found during the stage when
menstruation was absent and they are not menstruating. It is hard to say whether
they would all be menstruating under certain phases.

In 1929 a study was made by Hartwell on the healing of wounds, illustrating
the difference between the healing of subepithelial tissue and the epithelial cell,
and he showed that the epithelial cell portion of the wound heals differently from
that of the subepithelial tissue, in that the epithelial cells send out a substance
so that there is practically a regeneration rather than a scar tissue formation;
and that if this wound healing is modified, as it will be if it is subjected to
inflammatory reaction, then we get hornification and not only duplication of cells
but a tendency toward hyperplasia. It therefore seems that we can draw a direct
analogy between that and the sections which Dr. Sampson has shown us, where
there was a break between the tubal epithelium and those cells developing beyond.

DR. JAMES R. GOODALL, MONTREAL, CANADA.—It seems to me that Dr. Samp-
son's paper will cause us to change a great many of our beliefs. In the "spill"
theory, to which most of us adhered, it was thought that the epithelium may be
considered as a flower that carried with it its own soil. Today we have epithelium
changing its character, but where does its soil come from? The interstitial cells
of the uterus are unlike the glands. These are not present where the cells develop
in situ by the method which Dr. Sampson has outlined, but they are always present
in this type of endometriosis, and from what do they arise? We must assume
that they arise locally therefore, and if that is the case, it would be a basal mem-
brane or a basal cell which on one side develops into an epithelial cell and on
the other into an interstitial cell.

DR. GRETE STOHR, NEW YORK CITY.—In his preceding paper Dr. Sampson
has given a convincing interpretation of the genesis of certain forms of ectopic
endometroid structures. The variety in localization of these structures and the
variety of their morphology has advanced many attempts to explain this peculiar
newgrowth on a uniform basis.

Among other theories, Halban, in Vienna, has explained endometriosis by a
metastatic process, to which theory a case observed in the Woman's Hospital in
New York seems to furnish further evidence.

A white woman, forty years of age, was operated upon for menorrhagia due to

a large myoma uteri on September 21, 1931; her last menstruation occurred August 31. A diagnostic curettage, limited to the cervical canal, was performed preceding supravaginal hysterectomy. The gross examination of myomas and myometrium did not reveal anything unusual, only the endometrium appeared slightly hyperplastic. A portion of the uterine wall was subjected to microscopic examination and a moderate glandular hyperplasia of the mucosa with mild basal hyperplasia was found, beside a few bare glands of endometrial type scattered in the adjacent muscle layer. In a group of large vessels, seated in the peripheral area of the vascular layer of myometrium, the lumen of one of them is found occupied by a fragment of glandular tissue which simulates in all detail uterine mucosa and which reveals also the identical type found in the endometrium. The tissue fragment lies almost free in the lumen, only at a short area it is adjacent to the vessel wall, without exhibiting direct contact with it. In an adjacent vessel a solitary fragmented gland of endometrial type without stroma coat is seen and in another section of the series a destroyed, frayed bit of tissue, in which distinctly a few cells in epithelial arrangement are distinguishable, is found lying free in a large lymph space.

Single endometroid glands or epithelial cells within the lumen of lymph vessels in the uterus were observed by Halban, Lahm and Davidofsky, in no instance however, does the literature reveal an incidence in which intravascular fragments of whole endometrium were encountered.

Whether in our case the preceding curettage may account for the separation and intravascular propagation, is questionable. There are pros and contras for this assumption which for the limited time cannot be discussed here.

I referred to this case in the form of a preliminary report. As a singular finding I do not consider it as the final link in favor of the metastatic theory, but I believe it is convincing enough to prove that the genesis of hysteroadenosis has to be sought in different biologic processes.

DR. SAMPSON (closing).—Dr. Casler asked about the frequency of primary fimbrial endometriosis. I do not know its incidence either in patients with or without pelvic endometriosis in other situations, because only recently have I been able to recognize it with any degree of accuracy.

The paintings of these lesions, which are reproduced in this paper, portray their appearance better than any verbal description. I have found it of great help to place the tube, after its removal, in a dish of normal salt solution in order to float out the fimbriae. Since primary fimbrial endometriosis develops most frequently in the terminal portion of the tubal mucosa of the fimbriae at or near the junction of the mucosa with the serosa of the tube, that of the mesosalpinx and the germinal epithelium of the ovary when the ovarian fimbriae extend to that organ, it is important to carefully inspect the bases of the fimbriae. I have encountered it most frequently at the bases of the fimbriae of the lateral surface of the tube.

I believe it is only one focus from which secondary pelvic endometriosis may arise by direct extension and dissemination, and even though it should prove to be a relatively infrequent focus it is of importance in the composite picture of pelvic endometriosis.

DR. NOVAK (closing).—Dr. Taussig, it seems to me, presented a judicious summing-up of the present status of opinion concerning the etiology of endometriosis. Dr. Sampson's new study, as presented today, indicates that even the histologic approach to the problem is not exhausted, as do also the observations embodied in my own paper. The former established the fact that at least a certain proportion of cases of ovarian endometriosis are produced by a direct metaplasia of tubal mucosa into endometrium, with invasion of the ovary as a sequel. This is in accord

with my own observations, which indicate further that the germinal epithelium itself is capable of such metaplastic transformation into either a tubal or uterine type of epithelium. It would seem that, as a result of such demonstrations as those reported here today, ovarian endometriosis is explainable without invoking the theory of implantation of regurgitated uterine mucosa, although I believe that Dr. Sampson still feels that the latter factor is probably the important one in a proportion of the cases.

There is still, too, a question as to the mechanism concerned in the production of the often widely scattered areas of ectopic endometrium in cases of pelvic endometriosis. Are these also evidences of metaplasia, or are they to be explained on the implantation basis? I do not know. As Dr. Taussig has said, the two viewpoints appear to be gradually converging, and it seems possible that before many years have passed Dr. Sampson and I might well be able to present a joint paper on the etiology of endometriosis.

Selection of Appropriate Operation for the Cure of Prolapse, Dr. Robert T. Frank, New York City. (See page 574, October issue.)

DISCUSSION

DR. NATHAN SEARS, SYRACUSE, N. Y.—There has been a tendency recently to discredit the anatomy of the pelvic fascia as described by the anatomists, which is leading to considerable confusion among medical students. They are quite at a loss to understand the anatomy of the fascia around the vagina, the cervix, and the uterus. Personally I can see no more reason to doubt an orderly arrangement in the pelvic fascia than such an arrangement in the rest of the abdominal cavity or whatever part of the body may be studied. My own conception of the fascia is based upon surgical experience and dissection of four female pelves and briefly can be expressed as follows: Springing from and continuous with the superior levator fascia there is a double layer which rises into the pelvis; in the dorsal half of the pelvis it forms the uterosacral fold and in the ventral half of the pelvis it surrounds the cervix and the vagina.

DR. HAROLD O. JONES, CHICAGO, ILL.—At St. Luke's Hospital in Chicago, we have had a very definite attitude toward the pelvic tissues, including the uterus. We have felt that one of the indications for the selection of treatment was considerably influenced by the mortality of different procedures. Consequently, we have resorted to vaginal operations for the cure of these conditions. Of the cases operated upon by rather extensive operations for rectocele and cystocele, less than 300 Watkins' transposition operations, there was a mortality of 3. For cystocele and rectocele we have been satisfied with the type of procedure described by Dr. Frank and have had uniformly good success. The Watkins' transposition operation has been reserved for the very few cases that met the indications in this clinic, that is for the women past menopause who have rectocele. There has not been done in this institution a single suspension of the uterus for prolapse but they have all been satisfactorily treated by complete vaginal hysterectomy. The technic followed is that known as the Mayo procedure, with some modifications. After six of these cases where there was complete eversion of the vagina we had to completely obliterate this cavity. Three patients with complete prolapse had to have a subsequent operation. Two have urinary incontinence that occured after imperfect repair of the anterior wall, and one had a LeFort operation after considerable descent of the vaginal vault.

DR. GEORGE GRAY WARD, NEW YORK CITY.—In my opinion, the operation of suspension of the uterus to the abdominal wall to cure prolapse is not suitable.

It is popular with some men doing general surgery but not with many gynecologists. It is better to approach the problem from below according to my experience. I use in the cases of elderly women both the transposition operation of Watkins and the Mayo operation. The Watkins' operation I limit to those cases where the prolapse is not extreme. If the cases are properly selected we get very good results from that procedure. In the cases where there is a definite prolapse of the cervix, protruding from the orifice of the vagina and associated with a large cystocele, I prefer to do a vaginal hysterectomy with a modified Mayo technic, as Dr. Frank has mentioned, and we have satisfactory results in a large proportion of these cases.

Where I have found failure in that operation is that while we always cure the cystocele, we sometimes have an enterocele develop when there is a deep culdesac of Douglas present. If it is not obliterated it may later cause trouble. Therefore, in all of my cases I utilize the procedure of removing the peritoneal culdesac and uniting the uterosacral ligaments with interrupted linen sutures, thus obliterating Douglas' pouch. Our failures with that procedure are very few.

DR. JOSEPH L. BAER, CHICAGO, ILL.—In 1928 it was my privilege to report on a series of 212 patients operated upon for prolapse at the Michael Reese Hospital. At that time I analyzed the results and will not repeat them but would say that 41 per cent of all the patients were operated upon by the transposition method. I had hoped one of the discussants would mention the Halban procedure, whereby the vesical peritoneum is pulled out into the vagina until its fixed point on the parietal peritoneum is reached. The fundus uteri is attached to that parietovesical angle in the abdominal wall from below. The essential prerequisite is that the over-all length of the uterus be shortened to three inches by cervical amputation, and finally the reconstruction of the pelvic floor is done. It is applicable to women in the childbearing period as well as to those in the menopausal years. We have had no recurrences.

DR. FRANK (closing).—Dr. Sears brought out a valuable point. I feel that dissections in the vicinity of the bladder are extremely misleading because any anatomist can bring out certain structures to the detriment of others. All one has to do to realize this is to read the various anatomies. Although I do not decry the study of anatomy, I feel from the point of view of the operator that these points which I have tried to emphasize are most essential.

Referring to Dr. Jones' remarks, I did not bring out the mortality but it is extremely low. In simple cystocele and rectocele with the cervix in its normal position, we still do the anterior and posterior operation with success. The interposition operation we have reserved for cases of large cystocele where the cervix is well up in position. In older women with large prolapse we do vaginal hysterectomy and obliterate the Douglas' culdesac if it is protruding, as it is in the majority of cases. If ventral fixation could be performed without the danger of incisional hernia and without additional risk, I would consider it the ideal operation in most cases unless a pendulous abdomen were present.

Congenital Absence of the Vagina and Its Treatment, Dr. James C. Masson, Rochester, Minn. (See page 583, October issue.)

DISCUSSION

DR. P. BROOKE BLAND, PHILADELPHIA, PA.—Next to determining definitely the true nature of faulty anatomical development of the genital tract, especially with regard to the determination of sex, there is no anomaly or type of maldevelopment more pathetic or more distressing psychologically than rudimentary growth, or still worse, a total absence of the canal itself.

Dr. Masson pointed out and stressed the rôle psychology plays in these unfortunate

patients. In considering operative therapy in general, it may be accepted, I think, as axiomatic that in most, if not nearly all, surgical conditions the decision as to when a patient should or should not be operated upon rests squarely on the shoulders of the surgeon. There are, perhaps, occasions when the proposition may be left to the patient to decide. This may be found, for example, in the disorder described by the essayist.

One can readily understand how a patient acutely conscious of a gross architectural defect in the organs fundamentally concerned with reproduction could very readily become a victim of neurologic imbalance, and, hence, for psychologic reasons, if for no others, interference may not only be instituted but at times it may become absolutely necessary.

With respect to interference in an operative way for an absence of the vaginal canal, wholly or in part, save for neurologic indications, I personally can see no advantage of adopting the recourse, unless the patient contemplates wedlock or is already married. Even in these circumstances it is questionable whether an artificially constructed vaginal canal is ever satisfactory anatomically. From the standpoint of restoration of physiology, one may look upon the measure without much optimism, or no optimism at all. As a copulative canal it may suffice, but rarely if ever does it serve in a reproductional capacity. When the vaginal canal is absent, nearly all observers agree, I believe, that the structures in the pelvis beyond are likewise absent or so dwarfed as to be utterly functionless.

In view of these convictions, it would seem that those cases of alleged offspring ensuing after the formation of an artificial vagina followed some operative measure not in gross, but in minor forms of maldevelopment, as, for instance, an imperforate hymen or a moderate type of atresia in an isolated area of the lowermost segment of the genital canal itself.

I have never seen an absence of the vaginal canal, complete or partial, without a total absence or an exceedingly rudimentary uterine body, as noted in the five patients studied and reported by Dr. Masson.

With reference to the type of operation to employ in the face of gross anomalous development of the vagina, I probably have been somewhat tardy as well as timid in resorting to major abdominal surgery. In caring for these patients I have followed rather consistently a conservative course. On two occasions the Schubert procedure was performed. The primary operative results were fairly satisfactory, overcoming in one patient a rather tormenting nervous state, and in the other there was established a canal suitable for marital purposes.

In the few other patients, probably four or five in all, reconstructive plastic flaps were used. In one patient of this group the operation was carried out because of contemplated marriage. This, following the operation, was consummated and the patient subsequently succeeded in raising three lusty children, by adoption!

DR. ROBERT T. FRANK, New York City.—Until Dr. Geist and I had devised a technic free of serious risk, I was always unwilling to attempt the construction of a vagina. The mortality incident to the Baldwin and Schubert technic certainly is greater than 10 per cent, and to my personal knowledge, a number of fatal cases have not been reported in the literature. In my opinion, it approaches 20 per cent. We are at present working on our fifth case in which the first tube flap was completely unsuccessful. In spite of this, the patient was never in jeopardy, and we are now completing the final stage with the flap taken from the opposite side of the thigh. Three results now date back to approximately five years and have proved permanent and satisfactory. Another vagina of two and one-half years' duration is likewise satisfactory. The mere fact that this procedure takes longer than the Baldwin or Schubert technic should not prevent the choice of this operation as its entire freedom from risk more than counterbalances this drawback.

Intrauterine Radium Therapy as a Conservative Method of Treatment,

Dr. Walter T. Dannreuther, New York City.   (By Invitation.)
(See page 611, October issue.)

DISCUSSION

DR. ARTHUR H. CURTIS, Chicago, Ill.—Consideration must be given to the age which a patient should have attained before she is a fit subject for radium treatment of a malignant condition. I wonder whether we have not been making a mistake in accepting forty years as a satisfactory age limit? Should we not, as a routine, advance that age to at least forty-three or forty-four or even until the menopause is impending, rather than apply radium freely when the patient is as young as forty?

During rather recent times I have been confronted with a new pathologic entity, the occurrence of cancer in patients who during previous years have received radium as a therapeutic measure in nonmalignant conditions. I have personal knowledge of three of these patients; personal contact with two of them. The first came to me five years ago, at the menopause and bleeding. A diagnostic curettage was made and she was given approximately 2000 millicuries of radium within the uterine cavity. I examined the scrapings from the curettage and there was no suggestion of malignancy. Two weeks ago this patient returned to me with an incomplete obstruction of the cervical canal, with a little tarry discharge. I took her to the hospital, having no expectation that there would be serious trouble, and found an extensive adenocarcinoma of the body of the uterus. This patient may not have developed a cancer as the result of radiotherapy, but I suspect that this administration of 2000 millicuries was an indirect cause of its development because it caused obstruction of the cervical canal or that the cancer occurred as the result of endometrial irritation or a radium burn.

A second patient received a similar dosage, at the hands of another man, during her period of sexual activity, when she was about thirty. This was about twelve years ago. I saw her recently with an extensive carcinoma of the lower portion of the body of the uterus. A third patient was taken care of at Johns Hopkins Hospital in a similar manner.

DR ROBERT T. FRANK, New York City.—I am glad of this opportunity to make a preliminary report of a new method of treatment which has been introduced by one of our dermatologists at the Mt. Sinai Hospital in the treatment of hemorrhagic diathesis.

The successful attempt of Peck and Sobotka to control experimental purpura in animals with moccasin venom led Peck to treat patient with hemorrhagic diathesis with this substance. He noticed that in women with thrombocytopenic purpura the tendency to prolonged menstrual flow was checked by means of the snake venom injections. This led him to treat uterine bleeding of various types with this therapeutic agent. In collaboration with Dr. M. A. Goldberger, 12 selected cases of uterine bleeding were treated. The majority of these patients had been treated over a period of months or years by means of curettage, transfusions, and other means without lessening the tendency to bleeding. A number of the patients had to be hospitalized because of a marked secondary anemia, the hemoglobin being below 35 per cent. Three were puberty bleedings, 7 were functional uterine bleedings, 1 was a metrorrhagia in a patient with a submucous fibroid, and 1 was prolonged and profuse menstrual periods in a case of Henoch-Schönlein's purpura. In all of the cases there was a marked therapeutic effect with a reduction in the duration and amount of bleeding. The majority of the patients were treated while they were

still bleeding and the control of the bleeding was seen as quickly as thirty-six hours after the first injection in a few of the cases. It usually, however, required from seven to ten days for a therapeutic effect to be noted. The patients have been under treatment from two to five months. In 3 of the patients injections have been discontinued but the length of time is too short for us to decide whether it will be necessary to resume the therapy.

Method: The venom used was that of the moccasin snake (Ancistrodon piscivorus). It was put up in 1:3000 dilution and injected intradermally. The initial injection was 0.2 c.c. and the subsequent injections were 0.4 to 0.5 of a c.c. given twice weekly.

The local reaction is unpleasant but not of sufficient gravity to prevent the patients from returning for new treatments every five days.

DR. GEORGE GRAY WARD, NEW YORK CITY.—I wish to report an experience similar to Dr. Curtis'. A patient came to me some seven years ago, about at the time of menopause, having a uterus which was evidently enlarged, symmetrical, and with menorrhagia. It was a case selected for radiotherapy. She had the usual dosage of about 1500 milligram hours. This patient was perfectly well for seven years. She came into the follow-up clinic the other day with slight bleeding and a diagnostic curettage showed adenocarcinoma. The original pathologic findings at curettage were negative.

Another case of interest in this connection was that of a colored woman twenty years old who had never been pregnant, who had a fibroid of the uterus and excessive bleeding. Hemoglobin 15 per cent, 720,000 reds. She was given two transfusions and radium was used, 2000 milligram hours. She had complete amenorrhea for five months. She came in several months later pregnant and delivered a perfectly normal healthy boy.

The Treatment of Gonococcal Infections by Artificial (General) Hyperthermia, Drs. Stafford L. Warren, and Karl M. Wilson, N. Y. (See page 592, October issue.)

DISCUSSION

DR. C. FREDERICK FLUHMANN, SAN FRANCISCO, CAL.—I should like to draw attention to another method of producing hyperthermia, namely by the use of hot baths. This procedure was mentioned by the ancient Egyptians, Greeks, and Romans, but it is only within the past few years that it has been done while checked with a thermometer. Schamberg employed baths for sterilizing chancres and the method was further developed by Mehrtens and Pouppirt for the treatment of neurosyphilis. Dr. A. V. Pettit, one of my confrères at Stanford, conceived the idea of using it to treat gonorrhea and this study has now been conducted by him for a period of over two years. The patient is immersed in a hot bath, the temperature of the water being about 105° and gradually increased. The patient's temperature is taken every five minutes, and it can be raised to 104° or higher within a half hour. She is kept in the bath for a period of one hour, and one bath is given daily for four consecutive days. This, of course, is a hospital procedure, and each patient has a very careful preliminary examination, while an interne sits by the bath and watches her during the whole course of the treatment. Of 62 patients who have been treated to date, representing all types of inflammatory conditions of the pelvis, 38 are cured, 11 improved, 3 show no improvement, and 10 have had no follow-up. The criteria for a cure is that the patient must be well within three months, must show repeated negative smears, and have no demonstrable pathology in the pelvis.

Of considerable interest is the fact that the deep lesions are the ones apparently most readily influenced, while the superficial are most resistant. In preparation for the treatment the vagina should be scrubbed thoroughly with soap and water because if this is not done the patient may reinfect herself immediately afterwards since gonococci present in her vagina may survive. It would seem, therefore, that it is not only the effect of the high temperature on the gonococci which produces these good results, but some other factor which is induced by the hyperthermia.

DR. PHILLIP F. WILLIAMS, PHILADELPHIA, PA.—I would like to ask about the clinical applicability of this method of treatment, particularly in regard to two types of cases, gonococcal infections in pregnant women and in young children. In the majority of instances when a pregnant woman develops a febrile infection of high degree it frequently terminates the pregnancy. I should like to have Dr. Wilson's opinion as to whether pregnant women should be subjected to this method of treatment? One of the most difficult problems we have in the gynecology of childhood is the treatment of cervicitis, commonly called vaginitis, of young children and I would like to know whether Dr. Wilson feels that the extreme degree of hyperthermia that he has used would be advisable in the treatment of infants and young children?

DR. WILSON (closing).—We have not had enough experience with this method to be too specific about the results obtained. I did not have an opportunity to mention that in this series I presented one patient who had a lower birth canal infection, unknown to us, was pregnant at the time we treated her. She missed her following period and at the present time is approaching term without any damage. I do not recommend it as a therapy to carry out on a pregnant woman for I think it might be disastrous. One of those women reported we followed for over a year. She has since been pregnant and was delivered spontaneously and showed no trouble of any kind in the puerperium. This seems to me a good test of the permanence and efficiency of the cure. If we get a series of negative bacteriologic results and then a patient comes back with positive smears, one can never be sure that it is not a reinfection. We have had several examples of that.

We do not recommend this form of therapy as a routine treatment for gonorrheal infections at the present time. The technic must be much improved, but we do want to emphasize the principle of therapy, and that the usual strains of gonococci can be killed in the body on exposure to a temperature which can be tolerated by the patient, for a specific length of time. We are changing this technic already and during the last month or two we have a series of patients not included in this paper, and which have not been observed for a sufficient length of time to draw any conclusions, upon whom we have carried out the same principle of therapy but without any diathermy apparatus at all, using only radiant heat. It takes a little longer but the results are going to be equally satisfactory apparently and there is no danger of burning the patient. Several of our patients in this series did have small superficial burns at the point of contact with the electrodes.

I believe the ultimate technic will probably be a combination of local and general heat. One can raise the temperature to the desired level by local methods but it is so quickly dissipated by the blood stream that it will not be maintained for the requisite length of time to kill the organisms. If one elevates the body temperature to a somewhat lower level than we have shown here, say 40°, and supplements that by local heat at a higher level, it would be much easier for the patient and I believe the results will be equally satisfactory. It is the principle involved in the therapy, as I said, rather than the technic that I want to emphasize.

The Diagnostic Value of Radiopaque Contrast Media in Gynecology and Obstetrics, Drs. Alexander M. Campbell, J. Duane Miller, Thomas O. Menees, and L. E. Holly, Grand Rapids, Mich. (See page 542, October issue.)

DISCUSSION

DR. ARTHUR H. CURTIS, Chicago, Ill.—We must beware of the too frequent employment of lipiodol. There is considerable danger of producing at least a mild inflammatory intraperitoneal reaction. I have seen several patients treated with lipiodol elsewhere, in whom there was a marked inflammatory reaction. I therefore warned that we must not use lipiodol in cases other than those in which it is urgently necessary, such as preliminary to surgical work for relief of sterility. Lipiodol is of undoubted diagnostic value, but it must be used with caution.

DR. ROBERT T. FRANK, New York City.—I can only say that I am heartily in accord with what Dr. Curtis has stated. We have seen one pelvic abscess follow lipiodol injection. In another case in which it was necessary to open the abdomen a chronic peritonitis was found (due to encysted lipiodol) which involved the ovarian region. I believe lipiodol is harmful in cases of sterility. In consequence of such findings at my own clinic I have limited the use of lipiodol to cases where the tubes have previously been proved closed by air insufflation.

DR. CAMPBELL (closing).—When this paper is read it will be found to have covered all the criticisms mentioned. We brought out carefully the technic that should be employed and accentuated the care that should be taken in selection of cases. We do not believe that the use of lipiodol is any more harmful than any other diagnostic gynecologic procedure if it is carefully done in selected cases and in co-operation with a competent radiologist. We feel, however, that we must sound a note of warning against the indiscriminate use of uterosalpingography in the hands of those who neither understand its technic nor its contraindications. The same comment should apply to the use of amniography.

(To be continued in December issue)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY, 12, 1932

DR. E. EVERETT BUNZEL reported A Case of Marked Hydramnios in the Fifth Month of Pregnancy. (For original article see page 755.)

DISCUSSION

DR. G. H. RYDER.—Personally, I do not remember ever seeing marked hydramnios except with multiple pregnancy or abnormality of the fetus.

In the first 20,000 deliveries in the old Sloane Hospital, there were recorded 113 cases of marked hydramnios, an incidence of 1 in 177. Of these 20 were with twin pregnancies, 3 with triplets, and 5 with monstrosities. So that of the total 113 cases of hydramnios, 28, or 25 per cent were associated with multiple pregnancies or monstrosities.

In the whole series of 20,000 deliveries, there were recorded 244 sets of twins and 4 sets of triplets. Therefore, 8 per cent or 1 in 12 of all twin pregnancies, and 75 per cent or 3 out of 4 of all triplet pregnancies, showed marked hydramnios.

Of the 113 cases of hydramnios, 81 were in multiparae and 32 in primiparae. There were 62 abnormal presentations, and albumin was present in 65 or over half. Labor was premature in 49 and near term in 64.

There was no maternal mortality, but the fetal mortality was high. Of the 141 infants born, including multiple births, 65 were lost, or 46 per cent.

During the last year in private practice, I have had 3 cases of marked hydramnios. Two were in twin pregnancies and one was associated with a fetal monstrosity. Both twin pregnancies terminated spontaneously near the seventh month, 3 of the 4 infants dying of prematurity.

The case associated with fetal monstrosity is worthy of mention. A young primigravida, after slight nausea in early pregnancy and an attack of acute catarrhal jaundice in the fifth month, was seemingly normal until eight weeks from term, when she suddenly became greatly distended with liquor amnii. Her abdomen suddenly became the size of that of a woman at term. Severe Braxton-Hicks contractions precluded sleep. The cervix was well thinned out, one and a half fingers' dilated, with bulging membranes. Labor seemed imminent. But a two weeks' rest in bed with hypnotics and restriction of salt from the diet, caused abatement of all symptoms. The contractions ceased, the size of the abdomen diminished to that of a normal seven and a half months' pregnancy, and the cervix contracted down and closed. A week later, five weeks before expected confinement, labor started. This seemed normal, except that the uterus was asymmetrical, bulging out alarmingly on one side as though it might rupture. Full dilatation of the cervix soon occurred and the small fetal head was easily lifted out with forceps, but the correspondingly small body could not be delivered. After much difficulty, this was accomplished, and the cause of the trouble was seen to be an enormously distended fetal abdomen, the size of a football. The superficial veins around the navel were much distended. The child made only one or two feeble attempts at breathing. Autopsy showed a large dermoid cyst, adherent to the surrounding tissues and compressing the heart and lungs up into the thorax. The remaining fetal organs were normal, except that the ovaries were absent.

The most marked case of hydramnios that I have ever seen, occurred while I was resident at the Sloane Maternity Hospital. A country doctor telephoned that he had a pregnant woman with a "terrible malady." On admittance to the hospital, the patient presented a never to be forgotten picture. Her face was haggard and jaundiced, her abdomen was distended enormously, so that when she lay on her side with legs flexed, the dome of her abdomen extended as far out as her knees. The abdomen was so tense that the gentlest tap with the finger caused pain. Vaginal examination showed the cervix well thinned out and dilated 3 fingers, with tense bulging membranes. These were punctured and the cervix easily stretched to full dilatation. A small fetal back presented. A foot was grasped and a healthy fetus was easily delivered by the breech. A second sac of bulging membranes was found with a second fetus lying transversely. This also was delivered by the breech. The doctor guarding the fundus remarked that there was a third fetus. This also was delivered by the breech. Three healthy children were now kicking on an adjoining table, while three navel cords were hanging out of the mother's vagina, a most unusual sight. The two placentae were extracted manually and the uterus was packed with 5 per cent iodoform gauze, to prevent relaxation and hemorrhage. The three babies weighed together 17½ pounds. With the placentae and the enormous amount of liquor amnii this woman had been carrying a really tremendous weight. The mother made an uneventful recovery and all three children grew to adult life.

DR. R. M. BEACH.—I had practically the exact counterpart of the last case a number of years ago. The patient was about five months' pregnant, and I had the opportunity of observing her for three or four days. The abdomen increased an inch a day. The interesting symptom in her case was a very rapid pulse, from 130 to

140. She had three distinct syncopal attacks on the street due to this rapidly de-
veloping acute hydramnios. We took her to the hospital and ruptured the mem-
branes, but, unfortunately, she would not go into labor. We waited four or five days
and then did a vaginal hysterotomy, delivering a pair of twins. She made a very
good recovery.

DR. RAPHAEL KURZROK, by invitation, read a paper entitled **Biochemical
Studies of Human Semen—Factors Affecting the Migration of Sperm
Through the Cervix**. (For original article, see page 19, April, 1932,
issue.)

DISCUSSION

PROF. EDGAR G. MILLER, JR.—Dr. Kurzrok has very properly stressed the
view that there must be some orienting mechanism which starts the migration of the
sperm from the vaginal culdesac toward its destination in the fallopian tube. The
mere random swimming would seem to be inadequate. It is possible that the orgas-
mic reactions of the uterine muscle may in certain cases aid in the movement of sperm
into the uterus, but conception can occur without this mechanism. The phenomenon
described by Dr. Kurzrok offers a possible factor in the preliminary orientation of
the sperm migration on purely physicochemical grounds.

The mucus plug in the os would seem to offer a physical barrier to the migration.
However, its alkalinity favors sperm motility, and, once entered, the sperm are quite
able to swim in it. On the basis of the work reported, the mucus appears to have a
positive function in the orientation, and the maintenance of its normal alkalinity
seems to be a matter of some importance in this function. Because of its high
alkalinity (P_H 9.5) it has a very much greater concentration of hydroxyl ion, and
less of hydrogen ion, than the slightly alkaline semen in contact with it (P_H 7.8);
there is an even greater gradient of concentration of these ions at the interphase be-
tween the semen and the vaginal wall (P_H 3.6). Where these fluids, of different de-
grees of alkalinity or acidity, are in contact, there is naturally a tendency for the
ions to diffuse to establish equal concentrations. The hydrogen ion, with its positive
charge travels perhaps five times as fast as the average associated anion (negative),
while the hydroxyl ion, with its negative charge, travels perhaps four times as fast
as the average cation (positive). Consequently, there is a separation of positive and
negative charges, the mucus becoming more positive because of the hydroxyls leaving
it faster than the positive ions do, while the positive hydrogen ions are coming in
from the semen ahead of their anions; in the semen at the contact boundary the re-
verse is occurring. This builds up a difference of "electrical pressure." A potential
difference must occur in vivo at this phase boundary. Probably the "diffusion
potential" described is the most important factor; there are also other factors which
make it certain that a difference must occur. In vivo conditions cannot be exactly
duplicated in vitro. The potential differences measured (3-5 m.v.) were obtained in
vitro. I believe that they may be greater in vivo. Three to 5 m.v. may not seem to
be a very great figure; but when applied over a distance of, at most, probably 50
micra, it becomes a respectable gradient. And this gradient, as Dr. Kurzrok has re-
ported, will apparently cause a movement of the negatively charged sperm toward
the positive side of the gradient. This movement seemed to be a cataphoresis. It is
perhaps surprising, in view of results obtained by other workers on sperm of lower
animals, that galvanotropism was not observed.

I believe that, apart from the special application of this in the physiology of the
sperm in the tract, the most interesting point is that it offers a hypothesis to explain
how a so-called "chemotaxis" may occur.

Dr. Kurzrok has, I believe, presented a reasoning by analogy from in vitro experi-
ments that applies logically in the body. He has described what is probably one,

and perhaps not the most important, factor in a rather complex and largely un-known mechanism which determines the path of the sperm migration.

In reply to Dr. Moench's questions, the value of P_H 9.5 for the mucus is taken from other publications on the subject. Perhaps it is too high. However, the potentials reported were measured on normal material, and not calculated from theory. Moreover, acidification of the mucus destroyed the potential differences and pathologic, less alkaline mucus samples gave a similar reduction or even reversal. The voltage gradient seems to depend on the P_H gradient.

As to the question about thigmotaxis of sperm for oil droplets and other ''inert'' masses, no explanation is attempted. One suspects that surface tension phenomena are frequently involved. How far electrical forces may be called in explanation I do not know. The phenomenon described by Dr. Kurzrok seems, in our experience, to be unique for alkaline mucus.

DR. G. L. MOENCH.—In the marine animals there is a jelly which surrounds the ovum and the function of this seems to be to hold the sperm. I have often wondered whether the cervical mucus did not have a similar function.

I have not any apparatus to measure the potentials, but I took the cervical mucus and put it on a glass slide and found very much the same thing, namely that the sperm gathered at the junction of the mucus and the semen. I wondered whether that was simply due to the difference in viscosity and tried mineral oil and found they did exactly the same thing with the mineral oil as with the mucus; they gathered in a thick row at the border, and it seemed to me that at some point there was a physical break, but suddenly one would get through—the mineral oil not being a very good preservative—and after a while they got to wiggling and died. I then greatly increased the thickness by trying some of the various contraceptives on the market and found in those contraceptives where there was not any actual poison for the spermatozoa, they finally penetrated.

After referring to the penetrating qualities of the sperm and the mechanism of such penetration, Dr. Moench went on to say that he found the P_H of the cervix is lower than 9.5. I am not trying to contradict the biochemists at all, but I have taken it at the outside of the cervix where it is in contact with the vaginal P_H, and further up it is a little higher, so, after all apparently the P_H is between 9.5 and 3.5. I was able in one case to get a P_H in the vagina of less than 1.8. The potential of lactic acid being something like 0.5 and 0.8 that reduces the electrical charge very much. I do not think it influences the mechanism of the thing.

DR. W. H. CARY.—I have made a study of the behavior of sperm cells in the female secretions over a period of many years. Careful, postcoital, biologic investigations have been completed in well over 300 childless marriages. These observations indicate that sperm cells promptly and vigorously invade the inviting alkaline medium offered by the cervical secretion and that sperm migration is adversely influenced in direct proportion to the increased viscosity of this medium. The prompt occurrence of pregnancy in patients long sterile following some simple item of treatment, such as douching, the application of suppositories or tampons, or the passage of a sound, has doubtless taken place in the practice of many present and is to be ascribed to the correction of mild degrees of hyperviscosity. The large number of women who become pregnant in spite of habitual and prompt contraceptive douches would seem to indicate that the electrical influence which Dr. Kurzrok describes at the point of contact between the seminal pool and cervical secretions is most essential, at least, to sperm migration. These douches must either wash away the seminal pool or seriously alter its chemical character, and yet failure of contraception by douching is reported in as high as 33 per cent of these patients. Added experience has made me increasingly humble in attempting to explain the manifold influences during sperm migration. I feel certain, however, that the hazard which the viscosity of the cervical secretion normally exerts against migration of the sperm cells screens out weak and abnormal

cells from the invading host and that nature thus carries out its great principle of natural selection.

DR. KURZROK (closing).—The measurements of hydrogen ion vary quite markedly according to the type of apparatus used, whether it be a colorimeter or a glass electrode. Some of our experiments were carried out with a glass electrode while others were done with a colorimeter. The vaginal acidity is not a perfectly fixed thing. I believe that there are certain variations in it, depending probably upon the function of the ovary. What we want to stress is the fact that there is a potential gradient upward into the cervix and uterine cavity. As Dr. Miller said, we can not in any way duplicate in vitro the exact conditions that are present in vivo. We can only make relatively normal conditions.

In reference to the point raised by Dr. Cary as to how spermatozoa will manage to get up the cervix after a douche, I want to remind him first of all that a great many sperms may mechanically stick to the cervical plug of mucus. Many douches have a precipitating action on proteins and I can think for the moment of a possible precipitation of the surface of the mucus just beyond the point where the sperms have reached and what you have done there really is to seal off the sperm against further action of the douche. That is a possible explanation.

We have not solved this problem of migration: we have merely indicated a possible way. It is reasonable; it follows sound physiology, biology, and biochemistry. We have not explained the whole thing by any means. We have been trying to evolve some mechanism that may help us to understand the migration of sperm and in this way help us in some of the problems of sterility.

DR. ISIDOR C. RUBIN read a paper on the **Diagnosis of Peritubal Adhesions and Tubal Strictures by Uterotubal Insufflation.** (For original paper see page 729.)

DISCUSSION

DR. ROBERT L. DICKINSON.—May I ask if it is a fair inference that removal of the isthmus and reimplantation of a tube, as is done for some sterilities, will not so cripple the rhythmic contractions in the tube as possibly to make such an operation useless? There are thirty different operations of that kind and some of the most popular consist in sticking the shortened tube into the uterus and leaving the tube patent and supposing that a half a tube that is patent is nearly as good as a whole tube.

DR. W. H. CARY.—I desire to mention two points of possible interest to gynecologists who carry out patency tests without kymograph tracing. With proper apparatus and sufficient experience the physician should be able to make the patient entirely comfortable when ready to release the gas column, and the pressure should be raised so slowly that the operator may take cognizance of any subjective complaints by the patient and carefully record the location of pain and the gas pressure at which it occurs. The patient should be previously instructed to promptly report the site of any new pain during the test. Adhesions or obstructions at the outer portion of the tubes frequently reveal themselves by lateral pelvic pain at a gas pressure of approximately 120 mm. or more. Intramural occlusion does not commonly give this result. Secondly, bimanual examination should immediately follow the termination of insufflation. In certain abnormal cases a distended tube may be palpated. A primary drop in gas pressure may be due, one must remember, to the relaxation of intramural spasm even though the fimbria be closed.

DR. RUBIN (closing).—Dr. Dickinson is quite right. If one were to judge from that one case the operation is practically useless. It served the purpose of demonstrating what the ampullary portion of the tube will do, and that brings up a ques-

tion, namely, what one can accomplish by operation. This is not the time, however, to discuss this point.

Dr. Cary's suggestion is a very practical one. I have been able to locate the point of blockade by clinical tubal insufflation in practically all cases, which checked with the lipiodol examination.

In regard to the pressure at which pain is elicited, I find it varies but as a rule it takes more than 100 mm. of mercury to cause pain. It continues as long as the gas pressure is maintained, particularly if it rises to higher levels, and then it takes 30 or 40 mm. of drop to cause its disappearance.

A practical suggestion is in order. When a kymograph is not at hand it would be possible to plot out the curve described by the pressure fluctuations by watching the behavior of the mercurial column in the manometer. Of course, it is not as exact as the kymograph because the kymograph gives pressures in terms of time. The kymograph, after all, is an instrument of precision, and if one wants to arrive at accurate diagnosis of constrictions and tubal strictures, this instrument is indispensable.

CHICAGO GYNECOLOGICAL SOCIETY

STATED MEETING, JANUARY 15, 1932

Dr. Harry O. Maryan described **An Electrical Device for Grinding Tissue Under Aseptic Conditions**.

Dr. J. P. Greenhill presented a specimen of **Adenocarcinoma of the Ovary Associated With Pregnancy**.

This woman, a tertipara, aged thirty-three years, was admitted to the Cook County Hospital complaining of pain and a swelling in the abdomen, loss of weight and amenorrhea of three months' standing. During the past three years she had had various periods of amenorrhea. General examination was negative except for a slightly enlarged thyroid. The basal metabolic rate was plus 13. The abdomen was markedly distended. Two large masses could easily be felt. No fetal heart tones could be heard. On vaginal examination three large masses were easily outlined. One mass filled the culdesac, a second one felt like a three months pregnant uterus and on the right side was another very large, soft, cystic mass. The diagnosis made was pregnancy complicated by an ovarian tumor. X-ray examination proved to be negative for pregnancy.

At operation there was found a three and one-half months' pregnancy associated with a large ovarian tumor which measured approximately 20 by 15 by 15 cm. One-half of the tumor was solid and proved to be a papillary adenocarcinoma. The other half was a simple serous cyst. All over the abdomen as high up as the left kidney region there were metastatic nodules. The pregnant uterus, the tumor and the left ovary were removed. The case is reported because of a similar one presented by Dr. Danforth at the December meeting.

Dr. M. A. Schnitker (by invitation) and Dr. F. E. Whitacre presented a paper entitled **X-Ray Diagnosis and Fetal Death**. (Published in the *American Journal of Roentgenology,* September, 1932.)

Dr. Joseph B. De Lee presented a motion picture demonstrating the **Treatment of Breech Presentations**.

Drs. Cornell and Warfield presented a **Preliminary Report on the Use of Skiodan for Visualizing the Urinary Tract During Pregnancy.** (Published in this Journal, May, 1932, page 755.)

Department of Reviews and Abstracts

Selected Abstracts

Carcinoma

Bonney, V.: Surgical Treatment of Carcinoma of the Cervix. Lancet 218: 227, 1930.

The author encourages the use of the Wertheim operation, since his results with it are better than with radiation. His only exception is the inoperable group.

Radiation is not used in conjunction with operation but reserved for the inoperable cases.

In his series of 284 operations, 110 patients were well at the end of five years, while in 181, 55 were well at the end of ten years. The rate of cures is considerably changed when considered on the basis of glandular involvement: in 160 without involvement 81 were well, while in 124 with involvement only 29 were well after five years.

In 382 patients, 55 deaths occurred, 25 from shock and 15 from sepsis. Once the operation was completed in 27 minutes but speed is less of an objective. From his first 100 to his last 98 operations the operative mortality rate was lowered from 20 to 8 per cent.

About 68 per cent of the recurrences occurred within the first two years.

The writer feels that the true worth of this operation cannot be judged until it has been tried in other countries. This also applies to radiation therapy.

H. C. HESSELTINE.

Philipp, E.: Statistics on Carcinoma of the Cervix Uteri and of the Vagina of the Years 1923-1925. Zentralbl. f. Gynäk. 56: 212, 1932.

Statistics of 484 cases of carcinoma of the cervix and 15 cases of carcinoma of the vagina observed from 1923 to 1925 in Professor Stoeckel's clinic in Berlin are presented. The cases arranged themselves as follows: operable, 183 (40.8 per cent); borderline, 85 (19 per cent); inoperable, 180 (40.2 per cent).

Of this number, two of the inoperable cases were moribund on admission and died before treatment could be instituted. Of the remaining 446 cases 161, or 36 per cent, are well and free from recurrence. Classifying these cures according to the group into which they were placed at initial examination, it was found that: of the 183 operable cases, 105 or 57.3 per cent; of the 85 borderline cases, 27 or 31.7 per cent, and of the 178 inoperable cases, 29 or 16 per cent are well without recurrence.

Comparison between cases submitted to Wertheim operation, and those submitted to radiation gave the following results.

	OPERATION (131 CASES)		RADIATION (315 CASES)	
	NUMBER TREATED	PER CENT WELL	NUMBER TREATED	PER CENT WELL
operable	109	62.0	74	50.0
borderline	19	31.5	66	32.0
inoperable	3	0.0	175	16.6

Those cases treated by radiation gave an absolute percentage of healing as follows: 255 cases treated with radium alone, 74 (29.1 per cent), and 60 cases treated with radium and x-ray, 13 (21.7 per cent) are well without recurrence.

There were 15 cases of carcinoma of the vagina of which 3 were operable, 1 was borderline, and 11 were inoperable. One case from each group is well without recurrence, and all of these three cases were treated with radium.

WILLIAM F. MENGERT.

Begoin: Cancer of the Cervix and Hysterectomy. Ten to Twenty-five Year Results. Bordeaux Chirurgical 9: 1, 1930.

The author performed 75 radical Wertheim hysterectomies between 1904 and 1918. There were 6 operative deaths. Follow-up data were obtained on 40. Of these 20 are dead. Of the 20 still living and well, more than 20 years have elapsed since the operation in 5, more than 15 years in 5, more than 12 years in 5, and more than 10 years in 5 cases.

In reviewing the literature, the author has been unable to find many reports of statistics where the patients had been followed longer than 10 years. He was, however, able to collect 1,881 cases among which there were 7 instances of recurrence between 5 and 10 years after operation, while at the end of the 5 year period the patient had been apparently well. From this he concludes that although recurrence after 5 years may occur, it is comparatively rare and a 5 year cure may be considered as a complete cure.

THEO. W. ADAMS.

Weibel, W.: The Operative Treatment of Carcinoma of the Female Generative System. Med. Klin. 26: 117, 1930.

Among 2,000 cases of cancer at the Prag woman's clinic the distribution was as follows: Cervix of the uterus 80 per cent, body of the uterus 5.5 per cent, ovary 8 per cent, vulva 2 per cent, vagina 4 per cent and tube 0.25 per cent. The least malignant is cancer of the corpus uteri and the most malignant are cervical and ovarian carcinomas.

Operation should be radical in all cases except for cancer of the body of the uterus. In these cases a simple vaginal total extirpation is sufficient because the parametria are practically never infiltrated. The operative mortality is low and the percentage of cure high.

On the other hand, the operative mortality for cervical cancer is high and here also the vaginal approach is safer than the abdominal. The percentage of five year cures is not very high because a large proportion of the patients already have lymph gland metastases at the time of operation.

Weibel advises the vaginal operation for old and debilitated patients, for those with bad hearts and lungs and for early cases. For the advanced cases with parametrial and gland involvement, it is preferable to perform the radical abdominal operation.

For cancer of the vagina, an abdominal radical operation should be done. However, operability is low and permanent cures are few in number. For cancer of the vulva, an extensive operation must be performed.

In cases of ovarian carcinoma the operation should be radical and should be followed by radiation.

Cancer of the tubes has a most unfavorable prognosis for the chance of cure is only 4 per cent.

Every radical or palliative operation should be followed by roentgen ray treatment over a period of six to twelve months because there is no doubt whatever that postoperative irradiation in cancer of the female genitalia improves the chance of recovery.

J. P. GREENHILL.

Kamniker: The Improvement of Results in the Treatment of Uterine Carcinoma.
Wien. Klin. Wchnschr. 43: 943, 1930.

At the Peham clinic it has been found that the best results in the treatment of
the uterine carcinoma are obtained by utilizing operation by the vaginal route, post-
operative radium and x-ray therapy. There is a difference of 16 per cent in cures
between those who have had and those who have not had postoperative radiotherapy.
Considering this highly specialized form of treatment, the author strongly advises
the physician to refer patients with uterine carcinomas to clinics where the treat-
ment is available, in the hope that this will greatly improve the results obtained.

FRANK SPIELMAN.

Voltz: Physical Therapy in Gynecology. Therapie der Gegenwart 72: 29, 1931.

The author reports the results of radiation therapy at the Doederlein clinic. In
all 1319 patients suffering from carcinoma of the cervix were treated by radiation
during the years 1913-1923. Of these 225 or 15.4 per cent resulted in absolute five
year cures. These figures include all cases treated at the clinic, even those classi-
fied as advanced, hopeless or moribund on admission. During 1923-1925, 171 ad-
ditional patients were treated by radiation and 40 of these, or 23.3 per cent re-
sulted in absolute cures. This marked increase, the author feels, is due to im-
provements and refinements in technic. Of the Group I cases 41 per cent resulted
in absolute cures as compared with 23 per cent cures in Group II. Group III showed
11 per cent absolute cures and even in Group IV there were 9 absolute cures. It is
in these latter Groups III (the inoperable) and IV (the hopeless) that the results
obtained, though small, are striking for without radiation therapy, all of the pa-
tients in these two groups were doomed.

The results in corpus carcinoma were also striking. Of all patients with carcinoma
of the corpus uteri 41 per cent were permanently cured. Of the operable cases 66
per cent resulted in absolute cures; 10 per cent of those patients showing residual
growth following surgery were also cured. Vaginal carcinoma gave a 5 per cent
and vulvar carcinoma a 12 per cent cure.

These figures compare favorably with those in the literature of the world which
show 17.4 per cent cures for all cases and 42.7 per cent cures for cases in Groups
I and II. The absolute cures for corpus carcinoma in the literature is 35.6 per cent
for all types and 56.5 for the operable group.

Radiation therapy also gives excellent results in the treatment of menorrhagia
and metropathy. Here the operative mortality is still 5 per cent whereas Gauss has
reported 5,000 consecutive patients treated by radiation therapy with only 5 deaths.
The results furthermore were excellent, 95 per cent of patients with climacteric
bleeding resulting in amenorrhea. The same was true for 85 per cent of the
metropathies.

RALPH A. REIS.

**Bowing, H., and Fricke, E.: Results Obtained by Irradiation of Carcinoma of the
Cervix Uteri.** Journal-Lancet 51: 195, 1931.

The results obtained at the Mayo clinic by the irradiation treatment of cervical
cancer are presented. The cases are grouped as follow: (1) early or operable,
growth limited to cervical canal or part of the portio; (2) borderline, lesion in-
volving the entire face of the cervix frequently with extension to the vaginal walls;
(3) inoperable, infiltration of one or both parametria, frequently with fixation and
"frozen pelvis"; (4) modified, the lesion modified by previous treatment elsewhere
before the patient registered at the clinic; (5) recurring, recurrence following
operation or irradiation at the clinic. Of the cases treated from 1915 to 1924 in-

clusive, 1001, or 91.5 per cent, of the total number studied were traced. Those living after five years constituted 75 per cent of the early group, 61.53 per cent of the borderline, 21.49 per cent of the inoperable and 24.82 per cent of the modified. Lesions were also graded according to Broder's classification. Those graded three and four showed a slightly better survival rate than those graded one and two.

FRANK SPIELMAN.

deBuben, Ivan: Radium in the Treatment of Cancer of the Vagina. Surg. Gynec. Obst. **52:** 884, 1931.

As cancer of the vagina is a rare disease, there is not sufficient data on which to base a final opinion as to the value of radiotherapy.

Cancers of the vagina are exposed to a single dose of radium of 1,200 to 2,400 mg. hr. If examination shows an unsatisfactory result after six to eight weeks, the treatment is repeated. The lymphatic glands are treated with x-rays. Patients are examined once every six weeks for a while, then once every three months and later every six months.

The results obtained in the treatment of cancer of the vagina, whether by operation or by radiotherapy, are still far from satisfactory. The advantage of radiotherapy over surgery is that the latter has a wider range of applicability, also that at least temporarily its effect is palliative in most of the cases. The Wertheim method in patients who can be operated upon or total extirpation combined with the resection of rectum in cases with the growth in the posterior vaginal wall are considered to result in recovery most often. It is reasonable to hope, that by perfecting the methods of treatment and of the application of radium the results will not only be improved but the risk of recurrence will decrease.

WM. C. HENSKE.

Petit-Dutaillis, P: Considerations of the Beginning, Evolution and Treatment of Vulvar Epitheliomas. Based Upon Sixteen Observed and Treated Cases. Bull. de la Soc. d'obst. et de gynéc. **10:** 768, 1931.

Petit-Dutaillis reports 16 cases of vulvar carcinoma treated without any maternal mortality. In eight cases the epithelioma was limited to the vulva and there were no clinical manifestations of glandular involvement. Five of these cases were treated by total vulvectomy, two by total vulvectomy with subsequent radiation and one case was treated solely by means of radium. In eight cases the epithelioma had passed beyond the limits of the vulva. Two of these were treated by radium combined with surgery, whereas in the others only palliative treatment was given.

Vulvar carcinoma is one of the most serious forms of cancer and the incidence of cure is very small. Since in the author's series, half of the patients did not have any adenopathy it seems that vulvar cancer does not have any great tendency to extend to the lymph glands.

The author believes the best treatment for vulvar carcinoma is extensive removal of the vulva in a systematic way. Some individuals recommend a preliminary application of radium before operation. However, the author emphasizes that if radium is used, at least five or six weeks should elapse before the operation is performed. This is to prevent any unusual reaction in the cellular tissue and to avoid undue hemorrhage and lack of union of the sutures. However, the author does not believe the results obtained with preliminary radiotherapy justify its use. Certainly the loss of time involved should speak against it. Radiotherapy after operation however, is to be recommended.

J. P. GREENHILL.

Scott, E., and Oliver, M.: Primary Carcinoma of the Fallopian Tubes. J. Lab. & Clin. Med. 14: 429, 1929.

Since Webster's exhaustive article on primary carcinoma of the fallopian tubes in 1926, the authors have collected seven additional cases from the literature, and add two of their own. It is evident that primary carcinoma of the fallopian tubes is rare, and in comparison with the total pathologic lesions in this organ the percentage of malignancies is small. However, inasmuch as the condition is often recognized only histologically, cases certainly have been overlooked without microscopic examinations. Of the two cases reported, the first was a papillary alveolar carcinoma of the left tube and the second a similar carcinoma but not of the alveolar variety.

Both of these cases occurred in the postclimacteric period. The most common clinical symptoms of the disease are vaginal discharge, often bloody, pelvic pain, tumor mass and late in the disease, constipation and nocturia. The gross appearance of tubal carcinoma is often deceiving and its presence may be overlooked unless careful routine microscopic examinations are made. The microscopic picture is usually that of papillary alveolar carcinoma.

W. B. SERBIN.

Item

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The written examination of this Board held in various cities throughout the United States and Canada on October twenty-second consisted of the following questions.

1. Describe the circulation of the female pelvic organs.

2. What physiologic factors are responsible for the amenorrhea of pregnancy?

3. Describe the pathology of syphilis of the placenta.

4. Discuss the differential diagnosis of marginal and central placenta previa, and the treatment of the latter variety.

5. Describe the technic of internal podalic version and extraction.

6. What are the indications for cesarean section?

7. Discuss the use of pessaries in the treatment of retroversion of the uterus.

8. What are the contraindications for irradiation of fibromyomata of the uterus?

9. How do you treat carcinoma of the corpus uteri? Why?

10. Describe your operative technic in the removal of an intraligamentary cyst, 10 cm. in diameter, from the left broad ligament.

The general oral and clinical examination will be held in Los Angeles, December 7, 1932, immediately preceding the meeting of the Pacific Coast Society of Obstetrics and Gynecology. The names and address of successful candidates will be published in an early issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

The next written examination and review of case histories will be held in cities throughout this country and Canada, where there are Diplomates who may be empowered to conduct the examination, on April 1, 1933.

The next general, clinical examination is to be held in Milwaukee on Tuesday, June 13, 1933, immediately preceding the annual session of the American Medical Association. Reduced railroad rates will apply.

Early application is requested from those desiring to qualify for these examinations. For further information and application blanks address Dr. Paul Titus, 1015 Highland Building, Pittsburgh, Pennsylvania.

Books Received

CLINICAL ENDOCRINOLOGY OF THE FEMALE. By Charles Mazer and Leopold Goldstein. Illustrated. W. B. Saunders Company, 1932.

THE WISDOM OF THE BODY. By Walter B. Cannon, professor of physiology, Harvard Medical School. W. W. Norton & Company, New York, 1932.

THE HYGIENE OF MARRIAGE. By Millard S. Everett, Ph.D. Vanguard Press, New York, 1932.

PHYSIKALISCHE THERAPIE DER FRAUENKRANKHEITEN. Von Privatdozent Dr. Felix Gal, Zweite Universitaets-Frauenklinik in Budapest. Urban & Schwarzenberg, Berlin, 1932.

RECENT ADVANCES IN OBSTETRICS AND GYNECOLOGY. By Aleck W. Bourne and Leslie H. Williams. Third edition with 87 illustrations. P. Blakiston & Sons, Philadelphia, 1932.

SYNOPSIS OF GYNECOLOGY. By Harry Sturgeon Crossen, professor of clinical gynecology, Washington University Medical School, and Robert James Crossen, instructor in clinical gynecology and obstetrics. C. V. Mosby Company, St. Louis, 1932.

HANDBUCH DER INNEREN SEKRETION. Herausgegeben von Dr. Max Hirsch. I. Band, Lieferung 6. Curt Kabitzsch, Leipzig, 1932.

DER GEBURTSHIFLICH-GYNAEKOLOGISCHE SACHVERSTAENDIGE. Von Privatdozent Dr. Paul Huessy. Hans Huber, Bern-Berlin, 1932.

RECENT WORK ON PTOSIS OF THE FEMALE PELVIC VISCERA. By E. Hesketh Roberts, gynecologic surgeon, St. Johns Hospital, London. With 30 roentgenographs in plates, two illustrations in text and two tables. Dickson & Scudamore, London, 1931.

STUDIEN UEBER DIE VERAENDERUNGEN DER NACHGEBURT BEI LUES. Von T. E. Olin, assistent der dermatologischen Klinik in Helsingfors. Gustav Fischer, Jena, 1931.

THE EXPECTANT MOTHER. By Frederick C. Irving, professor of obstetrics, Harvard Medical School. Houghton Mifflin Company, Boston and New York, 1932.

LES DIAGNOSTICS ANATOMO-CLINIQUES de P. Lecène. Appareil Génital de la Femme. Seconde Partie. Par P. Moulonguet. Masson et Cie, Paris, 1932.

FORMFEHLER UND PLASTISCHE OPERATIONEN DER WEIBLICHEN BRUST. Von Dr. Erna Glaesmer in Heidelberg. Mit 48 Abbildungen. Ferdinand Enke, Stuttgart.

DER KUENSTLICHE ABORT. Indikationen und Methoden. Von Professor Dr. Georg Winter, Koenigsberg, und Professor Dr. Hans Naujoks, Marburg. Ferdinand Enke, Stuttgart, 1932.